FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Pulmonary-Allergy Drugs Advisory Committee

TUESDAY, MARCH 9, 2010

8:00 a.m. to 3:30 p.m.

Hilton Washington DC/Silver Spring

8727 Colesville Road

Silver Spring, MD

Pulmonary-Allergy Drugs Advisory Committee

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I N D E X

P R O C E E D I N G S

8:00 a.m.

DR. CALHOUN: Good morning. My name is Bill Calhoun. I'm from the University of Texas Medical Branch in Galveston, and I'd like to call this meeting to order.

At the beginning of the meeting, I think we'll start by introducing the panel members. And I believe we'll begin with Dr. Hubbard.

DR. HUBBARD: Yes. I'm Richard Hubbard from Pfizer, and I'm the industry representative on the panel.

DR. FOGGS: I'm Dr. Michael Foggs, Chief of Allergy and Immunology for Advocate Health Care, Chicago, Illinois.

DR. PLATTS-MILLS: I'm Tom Platts-Mills. I'm a professor of medicine at the University of Virginia.

DR. KRISHNAN: I'm Jerry Krishnan. I'm the Director of the Asthma/COPD Center at the University of Chicago.

DR. KNOELL: I'm Daren Knoell, professor of

pharmacy and medicine at the Ohio State University.

MS. GOTTESMAN: I'm Karen Gottesman. I'm the patient advocate.

DR. CARVALHO: I'm Paula Carvalho, professor of medicine, University of Washington.

DR. MAUGER: Dave Mauger, Division Chief, Biostatistics, at Penn State Hershey Medical Center.

DR. KHUC: Kristine Khuc, Designated Federal Official of this committee.

DR. HONSINGER: Richard Honsinger, clinical professor at the University of New Mexico School of Medicine, and I practice allergy and immunology in Los Alamos and Santa Fe, New Mexico.

MR. MULLINS: Rodney Mullins, the consumer representative; National Director, Public Health Advisors and Consultants.

DR. TERRY: Peter Terry, professor of medicine, Johns Hopkins.

DR. HENDELES: Leslie Hendeles, professor of pharmacy and pediatrics at the University of Florida.

MR. ZHOU: Feng Zhou, statistical reviewer for this application for Office of Biometrics.

DR. KARIMI-SHAH: Banu Karimi-Shah, the medical reviewer in the Division of Pulmonary and Allergy Products at FDA.

DR. CHOWDHURY: I'm Badrul Chowdhury. I'm the Division Director, Division of Pulmonary and Allergy Products, FDA.

DR. ROSEBRAUGH: Curt Rosebraugh, Director, Office of Drug Evaluation II.

DR. CALHOUN: Okay. Thank you. So to the panel members, please remember to turn your microphones on when you're speaking and turn your microphones off when you are finished.

For topics such as those being discussed at today's meetings, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their view without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until its conclusion.

I would like to remind everyone present, please, to silence your cell phones and other electronic devices, if you have not already done so.

The committee is reminded to refrain from discussing the meeting topic during breaks or lunch. Thank you.

At this point, Kristine Khuc will deal with the conflict of interest statement.

DR. KHUC: The Food and Drug Administration is convening today's meeting of the Pulmonary-Allergy Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug, and Cosmetics Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential conflict of

interest.

Under Section 712 of the Federal Food, Drug, and Cosmetics Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members and nonvoting members of the committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 USC Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussions related to New Drug Application 22-535, pirfenidone, manufactured by InterMune. The proposed indication of this drug is the treatment of patients with idiopathic

pulmonary fibrosis, scarring of the lungs without a known cause, to decrease the decline in lung function associated with this condition.

This is a particular matters meeting during which specific matters related to InterMune's pirfenidone will be discussed. Based on the agenda and all the financial interests reported by the committee members and temporary voting members of this committee, it has been determined that all interests and firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Richard Hubbard is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Hubbard's role at this meeting is to represent industry in general and not

any particular company. Dr. Hubbard is employed by Pfizer.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to exclude themself from this involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. CALHOUN: Okay. Thank you, Kristine.

We will now proceed with the opening remarks. Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meetings, FDA believes that it's important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee

presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based on the outcome of the meeting.

Likewise, the FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have such financial relationships. If you choose not to address the issue of financial relationships, it will not preclude you from speaking.

At this point, Dr. Chowdhury will have some introductory remarks.

DR. CHOWDHURY: Thank you, Dr. Calhoun.

On behalf of the FDA and the Division of Pulmonary and Allergy Products, I welcome you, members of the Pulmonary-Allergy Drugs Advisory Committee, the representatives of InterMune, and members of the audience, to this meeting. I hope we will have an interesting and productive meeting.

Today we will be discussing the new drug

application from InterMune, seeking approval for pirfenidone for the treatment of patients with idiopathic pulmonary fibrosis, or IPF, to reduce the decline in lung function. IPF is a chronic, progressive, diffuse parenchymal lung disease of unknown etiology that is uniformly fatal. There are no approved medications in the United States for the treatment of IPF.

The clinical program for IPF is challenging because there is no regulatory precedence, lack of validated surrogate endpoints and need for long-term studies.

I will give a high level summary of the clinical program to set the stage for subsequent presentations and issues for discussion.

There are two pivotal trials conducted by InterMune and submitted to the agency to support efficacy and safety of pirfenidone. The primary efficacy variable in both the trials was absolute change in percent predicted FVC from baseline to week 72.

Pirfenidone showed statistically significant

change for FVC, with an effect size of 4.4 percent over placebo in one of the two trials. The other trial did not show statistically significant change for FVC. Mortality benefit was not demonstrated in the trials, but was numerically favorable for some analyses.

On the safety side, pirfenidone was associated with gastrointestinal adverse effects, potentials for liver injury, photosensitivity, and rash.

I would like you to consider these and other efficacy and safety data as you listen to various presentations. Later in the day, you will deliberate on the efficacy and safety data and give us your view on approvability of pirfenidone.

Mr. Chairman, in closing, I would like to say that I appreciate the time you and everyone else in the committee has taken out of their busy schedule to advise us on this application. This is a reflection of your dedication and commitment to practice of medicine and public health.

Thank you. I will turn it back to you,

Mr. Chairman.

DR. CALHOUN: Okay. Thank you, Dr. Chowdhury. And just, again, to remind folks to disclose financial relationships, or the lack thereof, at the beginning of your presentation.

We will now proceed with the sponsor presentation from the InterMune folks.

DR. PORTER: Good morning. My name is Steve Porter. I'm the Chief Medical Officer at InterMune. On behalf of the sponsor, I'd like to thank the members of this committee, as well as FDA, for the opportunity today to present our data on the safety and efficacy of pirfenidone in the treatment of patients with idiopathic pulmonary fibrosis.

InterMune began its first clinical trial on IPF in the year 2000, and our discussion here today is the outcome of a 10-year commitment, in collaboration with patients, their caregivers, health care providers, and our colleagues at FDA, to address this devastating disease for which there are no medical treatment options.

I know that I speak for the entire

organization when I say we are truly delighted to be here today to present data on the first therapy that offers genuine hope to patients with this fatal condition.

Our proposed indication is for the treatment of patients with idiopathic pulmonary fibrosis to reduce decline in lung function. I'll begin our presentation today with a brief description of pirfenidone and an overview of the clinical development program.

Dr. Ron du Bois of National Jewish Health, Phase 3 protocol co-chair and an internationally recognized expert in IPF, will describe the disease of IPF and the need for new and effective therapies. Dr. Bill Bradford, Senior Vice President of Clinical Science and Biometrics at InterMune, will review the efficacy data supporting pirfenidone for the treatment of IPF.

I will then return to review the safety experience. And finally, Dr. Paul Noble of Duke University, protocol co-chair, who spent over 20 years treating and studying patients with IPF, will discuss

the benefit-risk. We'll then open the discussion up to your questions.

In addition to Drs. du Bois and Noble, we have several external experts, some of whom have been involved since the inception of the clinical development program, who are with us here today to help answer any questions you might have.

Idiopathic pulmonary fibrosis is a progressive, debilitating, and fatal lung disease of unknown etiology. As Dr. Chowdhury mentioned, in the United States, there are no approved treatments and there is no accepted standard of care. In fact, the only drug approved anywhere in the world is pirfenidone, which has been marketed in Japan under the trade name Pirespa, for IPF since 2008.

In the United States, current off-label treatments are unproven, and they have significant toxicities in many patients. And thus, there's an urgent and unmet need for new, effective, and safe treatments.

Now, pirfenidone is an orally available synthetic small molecule which exhibits anti-fibrotic,

anti-inflammatory properties in a variety of in vitro and animal models. Pirfenidone regulates TGF-beta and TNF-alpha mediated pathways. It has been shown to attenuate both fibroblast proliferation, as well as collagen deposition. And it's these preclinical observations that formed the initial rationale for the development of pirfenidone for IPF.

The hypothesis-generating study for pirfenidone in IPF actually came from an independent development program conducted by Shionogi, a global pharmaceutical company that owns the rights to pirfenidone in Japan.

The Phase 2 SP2 study was a randomized, double-blind, placebo-controlled trial completed by Shionogi in 2001. This was followed by SP3, a randomized, double-blind, placebo-controlled, registrational study conducted by Shionogi between 2004 and 2006. And it was this trial that subsequently led to registration of pirfenidone in Japan for the treatment of IPF.

The Phase 2 SP2 study also led to the design of the InterMune Phase 3 program, which consisted of

two concurrent randomized, double-blind, placebo-controlled trials, PIPF-004 and PIPF-006, which were conducted between 2006 and 2009. And throughout the presentation this morning, we will refer to these two trials as the 004 study and the 006 study, respectively.

In addition, InterMune is conducting two long-term, open label safety studies in IPF, the 002 study, which has been ongoing since 2003, and the 012 study, that is an extension study which enrolled patients completing the two InterMune Phase 3 trials.

The data on the efficacy and safety of pirfenidone that you will hear over the next hour has demonstrated substantial evidence of effectiveness for pirfenidone from the two InterMune Phase 3 studies. One of those studies, the 004 study, demonstrated benefit in the primary endpoint of change in percent predicted FVC, or forced vital capacity, and the secondary endpoint of progression-free survival.

The second study, 006, provided supportive evidence of a treatment effect, but as Dr. Chowdhury mentioned, did not achieve its primary endpoint.

Importantly, evidence of effectiveness was supported by multiple consistencies, both between and within these two studies. And finally, the overall clinical experience has shown a favorable safety profile for pirfenidone.

So in summary, the clinical development program, which is extensive for an orphan indication like IPF, has shown a clinically meaningful treatment effect with pirfenidone. And thus, we believe that pirfenidone is the first therapy to demonstrate a favorable benefit-risk profile in treating patients with idiopathic pulmonary fibrosis.

I thank you for your attention. Dr. Ron du Bois will now describe the disease of IPF.

DR. DU BOIS: Thank you and good morning, everyone. I'm Ron du Bois, pulmonologist at National Jewish Health in Denver, Colorado, and, with Dr. Paul Noble, co-chair of the steering committee of the pirfenidone program, I'd like to introduce idiopathic pulmonary fibrosis.

Of all the diseases that diffusely and progressively scar the lung, idiopathic pulmonary

fibrosis is the most common and the most lethal. There are considerable challenges to trying to identify an efficacious therapy for this condition. I'd like to highlight the extent of the problem, the nature of the disease, which makes clinical management tricky, and also adds complexity to clinical trial design.

By way of background, idiopathic pulmonary fibrosis predominately affects individuals who are greater than 50 years of age, and there's a predominance in males over females.

The incidence in the United States alone is thought to be roughly 30,000 per year, with a prevalence of 100,000 individuals. Strikingly and importantly, this incidence is increasing, and this increase is real. And as a consequence, the number of IPF-related deaths is also increasing.

In roughly a decade's period, more than 175,000 individuals died of IPF in the United States alone. These are the death numbers for men and women over that period. You will see that these are steadily rising year on year. Health and age-adjusted

mortality rates are increasing by roughly 30 to 40 percent. So this death rate is worse than most lung diseases, and indeed many cancers.

So what is idiopathic pulmonary fibrosis, and how does it impact upon the patient? Shown here is the normal, spongy, healthy architecture of a normal lung. And contrast this with this autopsy sample. This lung is destroyed, holes bounded by established fibrosis.

CT scanning builds up a three-dimensional picture of the anatomy of the lung, and reveals pretty identical processes. Here is a normal lung. The normal lung is aerated, which is why it's black, with the white structures being the normal vasculature.

Contrast again the CT section from a patient with idiopathic pulmonary fibrosis. On the left, there is no normal lung. These are holes with scar tissue. Nothing will make this better short of transplantation. To the right you see a similar, but less extensive pattern. There is some normal lung here, and buried within this will be some relatively early nascent pathology, because what this disease is

a disease of repetitive injury.

What is happening over time is the lung is injured and develops a fixed, scarred, fibrotic pathology. So that by the time a patient presents to a physician, much of the lung is fixed and fibrotic and injured, and there is relatively less nascent pathology that is amenable to any therapeutic intervention.

Now, the third and very important component of this disease is its heterogeneity. For any one individual, the rate of progression of this disease is highly variable and quite unpredictable. Patients can go through a period of stability and then decline, and vice versa.

Not only is this disease heterogeneous within an individual, it is heterogeneous between individuals. So nobody's disease necessarily marches along at the same pace as others.

However, no matter what the timeline, virtually every patient will decline insidiously. Patients become increasingly housebound, oxygen-dependent, and then wheelchair-bound, and ultimately

die. And this is the most horrendous thing, both to experience and to witness, the most appalling disease.

So the nature of idiopathic pulmonary fibrosis, given that at presentation, patients will have a lot of established disease with relatively less nascent disease amenable to therapy, the impact of treatment needs to be viewed realistically in this context. That destroyed, fixed, fibrotic lung cannot be repaired; and so realistically, the best that one might hope to achieve is slowing of the rate of progression, and, ideally, stabilization of the disease process.

So how can this be measured? There's little in the background literature to help guide us on this. There are very few trials of the appropriate size, design, that give us clues. About 10 years ago, the American Thoracic Society and European Respiratory Society set out some guidelines to try to help with diagnosing this disease and monitoring it.

While they raised a number of potential indices to be followed to assess change, no specific guidelines on which endpoints to use in clinical

trials emerged. As we've already heard, we have no regulatory precedent to use as a template.

With this background and in this context, I would suggest to you that pirfenidone has been -- the pirfenidone program has been in the vanguard of clinical trial design process and conduct.

So how to choose an endpoint with this background? The steering committee agonized long and hard on all of the indices that were set out by the ATS/ERS guidelines for monitoring to see which of these would be the most robust. And I'd like to provide some data that would support the concept that the forced vital capacity change is robust and clinically meaningful, and of clinical relevance.

As I hope I've indicated, IPF is a disease of lung scarring. When the lung scars, it gets smaller. Forced vital capacity is a measure of lung size. But when it's gone in this disease, it's gone. It doesn't come back. So there's irreversible morbidity that forced vital capacity measures in a quantitative fashion. As I've said, it's widely used by ATS, and is regarded by ATS/ERS as the most robust

index to follow, because it's a reliable, repeatable measure.

I believe that the clinical meaningfulness of this endpoint index is illustrated by several performance characteristics. It is reliable. It's repeatable. It's a test that's relatively easy to do. And the repeatability means that there's very little by way of noise from technical measurement issues.

It's valid. Severity of forced vital capacity diminution correlates with breathlessness and health-related quality of life scores, indices, I would suggest, that are of great clinical relevance to the patient. And also, it's a responsive measure. So changes in forced vital capacity are reflected in other indices, again, of relevance to the patient, including health-related quality of life.

But changes in forced vital capacity are also associated with subsequent mortality. Does this mean that forced vital capacity causes death? I think it's difficult to say this. But what I can say is that if forced vital capacity is reduced year on year, once it reaches 40 percent, everybody's dead. And so

the pace at which this threshold is achieved is very important for patients.

I'll just show you here some data to illustrate the mortality point. In the top of the slide, I'm showing changes of forced vital capacity of a categorical nature. If a patient loses more than 10 percent of forced vital capacity, there's almost a threefold risk of death in the subsequent year. This is over a 24-week period, this decline, based on data from two very large studies of Interferon gamma.

But interestingly and intriguingly, lesser changes of as little as 5 percent can also predict subsequent one-year mortality. And in the bottom, you see, by contrast, that the baseline changes, although of some significance, are much less potent than the change in forced vital capacity as an index of risk of death in the subsequent year.

So in addition to these issues of clinically meaningful endpoints, I'd like to just say one word about the magnitude of the change. Now, as a clinician, I look at clinical trial data and I look at what appear to be perhaps modest changes in a pace of

decline of a process between those individuals on active drug and on placebo.

But, of course, I don't treat mean changes. I see individual patients. So if I see something which suggests a divergence, it's crucial to take this down to the patient level where categorical changes, as I hope I've indicated, are very much more meaningful.

So categorical changes of FVC, for example, by 10 percent, are very meaningful changes for patient health, symptomatology, and quality of life indices. And progression-free survival is a similar categorical analysis that is of huge relevance, obviously, to the patient.

I'd like to also suggest to you that the magnitude of mean change does not always reflect the magnitude of the benefit that individual patients might achieve with a novel therapy.

So by way of conclusion, what I've tried to set out for you is that this is a horrible disease. This is a progressive, attritional disease that destroys lung and causes fixed fibrosis. In the

United States, there are no approved therapies for this disease, and indeed very little in the pipeline that will achieve licensing within the next several years.

It's a heterogeneous disease. Individuals progress at a different pace. In any one study, there'll be a number of individuals whose disease has been stable. And therefore, categorical changes within an individual are important measures to consider.

I believe there are urgent needs for treatment for this condition. Every time I speak with a patient, I'm asked, "When will we have something new, Doctor?" And I believe that the pirfenidone program has addressed the complexities of this disease process, the individuality of this disease process, the nature of this disease process, and has chosen an endpoint that means something of value to the individuals affected by this disease.

So I'd like to thank you very much for your attention, and I'd like to invite Dr. Bill Bradford to the podium to discuss the efficacy data.

DR. BRADFORD: Thank you, Dr. du Bois. Good morning. I'm Bill Bradford, Senior Vice President of Clinical Science and Biometrics at InterMune. Today, I'm pleased to have the opportunity to share our efficacy findings in support of the approval of pirfenidone.

Let me first summarize the evidence which we believe demonstrates the clinical benefit of pirfenidone. Our first pivotal study, 004, demonstrates a robust and persuasive result on the primary endpoint and two clinically important secondary endpoints. The second pivotal study, 006, further supports 004 with noteworthy consistencies across studies, although the primary endpoint was not achieved.

The pooled results of 004 and 006 provide precise estimates of clinically meaningful effects on percent predicted forced vital capacity, progression-free survival, and 6-minute walk test distance. We believe this collective evidence demonstrates the clinical benefit of pirfenidone in patients with IPF.

My presentation today is divided into three

parts. I'll begin with a brief overview of the Shionogi studies, SP2 and SP3, which were instrumental to the design of the InterMune studies. Next, I'll review the efficacy findings from the two InterMune pivotal studies, 004 and 006, and offer several direct comparisons of data across those studies. Lastly, I'll review pooled analyses of the 004 and 006 studies.

Let us look first at the Shionogi studies. SP2, Shionogi's initial proof of concept study, was a 52-week, randomized, double-blind, placebo-controlled trial conducted in Japan. This study was terminated early based on efficacy favorable to pirfenidone in an interim analysis. The vital capacity endpoints favored pirfenidone, an observation suggesting the drug reduces decline in lung function.

This observation led to the initiation of three Phase 3 studies, one by Shionogi and two by InterMune. Let's look first at the Shionogi Phase 3 study.

SP3, like SP2, was a 52-week, randomized, double-blind, placebo-controlled trial conducted in

Japan. Patients were randomized with 2:2:1 probability to pirfenidone 1800 milligrams a day, placebo, or pirfenidone 1200 milligrams per day. The primary efficacy comparisons were between the high dose and the placebo.

Eligibility required a confident diagnosis of IPF, confirmed by an expert central review panel, and a mild to moderate level of impairment in lung function. The primary endpoint was change in vital capacity at week 52.

In the SP3 study, the primary endpoint was achieved, a p-value of 0.042. Progression-free survival, one of two key secondary efficacy endpoints, was defined as time to death or a 10 percent decrement in vital capacity. This endpoint was also achieved, with a hazard ratio of 0.64, representing a 36 percent reduction in risk, and a p-value of 0.028.

As you can see from the plots of both these endpoints, the treatment effect emerges early in the study and persists out to week 52. The results of SP3 confirmed those of SP2 and led to the approval of pirfenidone in Japan for the treatment of patients

with IPF.

Before turning to the InterMune studies, I'd like to briefly overview how we utilized the findings of the Shionogi studies, and, in particular, SP2, which was complete at the time we designed our program.

Part of our approach in the design of our pivotal studies was to leverage the learnings of the SP2 study. We consciously conserved several key design aspects of this study in our own Phase 3 effort.

First, we chose to study patients with mild to moderate impairment in lung function. These patients are most likely to benefit from an intervention that slows the irreversible loss of lung function seen in IPF. This is also the patient population in which Shionogi established proof of concept.

Next, we chose a primary endpoint of change in lung function measured by forced vital capacity. This is clinically important endpoint, as you just heard from Dr. du Bois, and very similar to the

Shionogi endpoint of vital capacity.

Lastly, we chose the 2403 milligram-per-day dose by normalizing the Shionogi dose to expected body weights of the predominately U.S.-based study population.

Let me now review the efficacy findings of the two InterMune pivotal studies, 004 and 006. These studies were nearly identical in design. I'll begin with the 004 study.

It was a multinational, randomized, double-blind, placebo-controlled trial. Patients were randomized with 2:2:1 probability to pirfenidone 2403 milligrams per day, placebo, or pirfenidone 1197 milligrams per day.

Study treatment and study assessments were to continue until 72 weeks after the last patient was enrolled. Importantly, patients permanently discontinuing study treatment were to continue with study assessments, and to have such assessments included in the intent-to-treat analyses.

Eligibility required a confident clinical and high-resolution CT diagnosis of IPF. In patients

not meeting protocol criteria for definite IPF on the HRCT, a confirmatory surgical lung biopsy was required. FVC and DLCO criteria targeted patients with a mild to moderate level of impairment in lung function, and excluded were patients with obstructive lung disease and patients on medications for IPF.

Primary efficacy endpoint was percent predicted FVC change at week 72. FVC was assessed at baseline and at regular 12-week intervals throughout the study period under a rigorous protocol based on ATS guidelines.

The primary efficacy analysis was a rank ANCOVA performed in the intent-to-treat population. Deaths, representing the worst possible clinical outcome, were assigned the worst ranks, while all other missing data was imputed based on observations in similar patients with non-missing data.

The magnitude of the treatment effect was estimated on the population level by the difference in treatment group means. On the patient level, treatment effect was analyzed based on categorical change in FVC. The categorical analysis assesses the

proportion of individual patients experiencing clinically meaningful changes in forced vital capacity.

At the time our pivotal studies were designed, there was limited experience to guide the selection, powering, or prioritization of efficacy endpoints in IPF clinical trials. Shown here is the spectrum of secondary endpoints that were pre-specified. The strategy here was to explore the pirfenidone treatment effect across a range of endpoints reflective of the different domains of the IPF disease process.

We also pre-specified several exploratory endpoints. However, given its clinical importance, I'll focus on the survival outcome.

Four hundred and thirty-five patients were randomized into the study. Over 80 percent of patients in each group completed study treatment. This is a high proportion, considering the length of the study and the gravity of the disease state. Treatment discontinuations due to adverse events were more common in the pirfenidone group, while

discontinuations due to deaths were more common in the placebo group.

Over 90 percent of patients in each group completed the study. This is another high proportion, which minimizes concerns around the handling of missing data.

The demographic and baseline characteristics were well-balanced across study groups. Mean age was in the mid-60s, consistent with the epidemiology of IPF. And approximately a third of patients were enrolled at sites outside the U.S.

The mean FVC and DLCO were reflective of a mild to moderate level of impairment in lung function. Less than 20 percent of patients were on supplemental oxygen. Over 90 percent of patients met protocol criteria for definite IPF on the HRTC, underscoring the high level of confidence in the diagnosis. The primary efficacy endpoint, percent predicted FVC change at week 72, was convincingly met in the 004 study, with a rank ANCOVA p-value of 0.001.

Shown here is the mean change from baseline at percent predicted FVC over the duration of the

study period. The pirfenidone 2403 milligram-per-day dose group is in blue, and the placebo in orange. The table beneath the figure summarizes the treatment effect based on treatment group means. At week 72, there was a 4.4 percent absolute treatment group difference, representing a 35 percent relative difference.

As you can see from the plots, the treatment effect emerges early in the study, increases in magnitude, and persists out to week 72. The outcomes in the low-dose group were immediate to the high-dose and placebo groups, providing evidence of a dose-response relationship.

This positive result on the primary endpoint is supported by positive results on several clinically important secondary endpoints, which I'll now review.

First, an analysis of categorical change in percent predicted FVC was performed based on a five-level scale, as detailed in the briefing document. Importantly, this analysis assesses treatment effect at the individual patient level, in contrast to the difference in treatment group means, which is a

population metric.

This figure summarizes these results based on two clinically important thresholds of change, declines greater than 10 percent, and no decline. Declines in FVC greater than 10 percent are widely reported in the medical literature as being clinically important and highly prognostic for survival outcomes.

Based on this threshold, only 20 percent of pirfenidone patients progress compared with 35 percent of placebo patients. Correspondingly, 24 percent of pirfenidone patients experience no decline, compared with 14 percent of placebo patients. This analysis, with a p-value of 0.001, provides strong evidence of a clinically meaningful treatment effect on forced vital capacity.

The next secondary endpoint, progression-free survival, was defined as time to death or confirmed disease progression, with disease progression requiring a 10 percent decrement in percent predicted FVC or a 15 percent decrement in percent predicted DLCO. This endpoint resulted in a hazard ratio of 0.64, representing a 36 percent

reduction in risk and a p-value of 0.023.

As you can see from the Kaplan-Meier plots, the treatment effect emerges early in the study and persists beyond week 84. The time points to the far right of the figure should be interpreted with caution, owing to the relatively few subjects remaining at risk.

Again, the outcomes in the low-dose group were intermediate to those in the high-dose and placebo groups, providing further evidence of a dose-response relationship.

Here's a summary of the standardized treatment effects for all the secondary endpoints in the 004 study, including categorical FVC change and progression-free survival. In the forest plot, the circles denote the point estimates and the horizontal bars the 95 percent confidence intervals around those estimates.

While the other secondary endpoints did not achieve nominal p-values less than .05, it is noteworthy that the directionality effect favors pirfenidone over placebo for all of these endpoints.

To summarize, the 004 study was robust, exhibiting excellent study conduct with a high rate of patient retention. The 004 study demonstrated benefit on the primary endpoint of percent predicted FVC change.

Further, a clinically meaningful treatment effect was observed on both categorical percent predicted FVC change and progression-free survival. Finally, a dose-response relationship was observed, which supports both the overall efficacy findings and the selection of the high dose.

Let us now look at the results of the second pivotal study, 006. This was a multinational, randomized, double-blind, placebo-controlled trial in which patients were randomized with equal probability to pirfenidone 2403 milligrams per day or placebo. The study design and study conduct were otherwise identical to 004, with the exception of one additional secondary endpoint, HRCT change in fibrosis at week 72.

Three hundred and forty-four patients were randomized into the study. And as we saw in the 004

study, approximately 80 percent of patients in each group completed treatment. Discontinuations due to adverse events were more common in the pirfenidone group, while discontinuations due to death were more common in the placebo group. Again, over 90 percent of patients completed the study.

The demographic and baseline characteristics were well-balanced across the treatment groups. The mean FVC and DLCO, as we saw in 004, were consistent with a mild to moderate level of impairment in lung function.

The primary efficacy endpoint, percent predicted FVC change at week 72, was not achieved in the 006 study. At week 72, there was no evidence of a treatment effect, with only a 6.5 percent relative difference between the two treatment groups.

There is, however, evidence of a treatment effect at time points out through week 48, where we observe a 1.9 percent absolute treatment group difference. This represents a 27 percent relative difference, with a nominal p-value of 0.005.

While the primary endpoint was not achieved,

the secondary endpoint, a 6-minute walk test distance change, does provide clear evidence of a pirfenidone treatment effect. At week 72, a 32-meter absolute treatment group difference was observed, representing a 41 percent relative reduction, with a rank ANCOVA p-value less than 0.001. Of note, the treatment effect emerges early, increases in magnitude, and persists out to week 72.

Here's a summary of the standardized treatment effects for all the secondary endpoints in 006, including a 6-minute walk test distance. None of the other endpoints achieved a nominal p-value less than .05. However, the point estimates are all either neutral or favor pirfenidone over placebo.

To summarize, the 006 study exhibited excellent study conduct, with high rates of patient retention. Primary endpoint of percent predicted FVC change at week 72 was not achieved. However, a treatment effect on percent predicted FVC was observed at time points through week 48. A clinically meaningful treatment effect was observed on the secondary endpoint of change in 6-minute walk test

distance.

Given the similarities in design and conduct of the two pivotal studies, the differing primary endpoint results at week 72 are perplexing. In an effort to better understand these results, we've conducted a number of direct comparisons of data across the two studies. We've also conducted extensive exploratory analyses. I'd like to review these data with you now.

Here's a summary of the landmark analyses of percent predicted FVC change at each study assessment time point. In the 004 study, as we saw previously, the treatment effect emerged early, increased in magnitude, and persists out to week 72. Now, let us compare this result with the results of the 006 study.

In 006, we, again, see a treatment effect emerge early in the study and persist out to week 48, with all these early time points showing a high level of consistency across the two studies. At weeks 60 and 72, while the treatment effect is stable in the 004 study, it attenuates in the 006 study. However, the point estimates continue to favor pirfenidone over

placebo, and the confidence intervals are largely overlapping.

In this type of situation, a repeated measures analysis may prove useful to further explore treatment effect. Let me share the results of that analysis with you.

Repeated measures analysis was pre-specified for each study to evaluate the average treatment effect over the full duration of the study period. Shown here are the standardized treatment effects from the repeated measures analysis based on ranked percent predicted FVC change.

Pirfenidone reduced the average decline in FVC in both studies, with a similar magnitude of effect. The nominal p-values for these analyses in 004 and 006 were p less than 0.001 and 0.007, respectively. These analyses highlight the overall consistency in the FVC findings across the two pivotal studies.

When the 004 and 006 studies were designed, there was no meaningful data on the performance characteristics of the 6-minute walk test in patients

with IPF. Since then, three independent studies have estimated the minimal clinically important difference to be less than 50 meters. Decrements greater than 50 meters have also been shown to be highly prognostic for survival.

Given this newly emergent data, we conducted a post hoc analysis on the proportion of patients experiencing 50-meter decrements. As you can see from this figure, fewer pirfenidone than placebo patients experienced 50-meter decrements in 6-minute walk test distance in both the pivotal studies, and there was a similar magnitude of treatment effect across the two studies.

We have conducted extensive exploratory analyses in an effort to better understand the differences in week 72 FVC outcomes. We've analyzed demographic and baseline characteristics, patient disposition, concomitant medications, and numerous other variables using a variety of analytic techniques.

Based on these analyses, the differences are not clearly explained by imbalances, in effect,

modifiers, across the two studies. Rather, we believe the overall differences are likely related to the intrinsic variability in rates of FVC decline in this heterogeneous disease.

In the final few minutes of my presentation, I'd like to review the pooled analyses of the primary and secondary endpoints in the 004 and 006 studies. These analyses were pre-specified for the integrated summary of efficacy, and should be considered exploratory in nature.

There were several good reasons for conducting these analyses. First, at the time the pivotal studies were designed, there was very limited preliminary data to guide the powering of endpoints. Second, we consciously designed 004 and 006 as nearly identical studies to facilitate pooling.

Next, the individual study results support pooling. The overall results are directionally similar, and there's no treatment by study interaction. Lastly, the pooled results provide the most precise estimates of effect.

In the pooled analysis of the primary

efficacy endpoint, percent predicted FVC change at week 72, there's a 2.5 percent absolute treatment group difference. This represents a 23 percent relative reduction, with a p-value of 0.005.

Here's a summary of the standardized treatment effects, from the pooled analyses, all the secondary endpoints in 004 and 006. Of note, the point estimates for all of these endpoints favor pirfenidone over placebo.

I will now individually review the results for the three endpoints that achieved a nominal p-value less than .05 in one of the pivotal studies.

In the analysis of categorical FVC change at week 72, only 22 percent of pirfenidone patients experienced a 10 percent decline, compared with 31 percent of placebo patients. Correspondingly, 25 percent of pirfenidone patients experienced no decline, compared with 18 percent of placebo patients.

In the pooled analysis of progression-free survival, we observed a hazard ratio of 0.74, representing a 26 percent reduction in risk, with a p-value of 0.025. As you can see from the Kaplan-Meier

plots, the treatment effect emerges early and persists beyond week 84. Again, the time points to the far right of the plots should be interpreted with caution, owing to the relatively few subjects remaining at risk.

The last secondary endpoint I'll review is 6-minute walk test distance. In this pooled analysis at week 72, there's a 24-meter absolute treatment group difference, representing a 31 percent relative difference, with a rank ANCOVA p-value less than 0.001.

Finally, let us look at the exploratory endpoint of survival. In the pre-specified analysis of all-cause mortality, a hazard ratio of 0.77 with a p-value of .315 was observed. The hazard ratio in the analysis of IPF-related mortality was 0.62, with a p-value of 0.117.

We also conducted analyses of on-treatment mortality as part of the safety evaluation. These analyses included deaths occurring up to 28 days after the last dose of study treatment.

In the analysis of all-cause mortality,

there's a hazard ratio of 0.65, with a p-value of 0.141. And importantly, the hazard ratio in the analysis of IPF-related mortality was 0.48, with a p-value of 0.30. These findings suggest that the observed reduction in all-cause mortality is driven by a reduction in IPF-related mortality. Despite this relatively small number of deaths, the magnitude of the mortality effect supports the other efficacy findings for pirfenidone.

Let me now summarize our overall efficacy findings. The 004 study demonstrated benefit on the primary endpoint of change in percent predicted FVC at week 72. Clinically meaningful effects were observed on the secondary endpoints of categorical change at percent predicted FVC and progression-free survival, providing additional evidence of benefit.

The 006 study did not achieve its primary endpoint at week 72. However, evidence of a pirfenidone treatment effect on percent predicted FVC consistent with the 004 study was observed at time points through week 48 and overall in the repeated measures analysis. A clinically meaningful treatment

effect was also observed on 6-minute walk test distance.

Pooled analyses of 004 and 006 studies provide the most precise estimates of the magnitude of the treatment effect. These analyses showed a clinically meaningful treatment effect on percent predicted FVC, progression-free survival, and six-minute walk test distance. The observed dose/response relationship in the 004 study supports the overall efficacy findings and the selection of the high dose.

In conclusion, we believe the collective evidence from these studies, including the robust and statistically persuasive results from the 004 study and the supportive results from the 006 study, demonstrate the clinically meaningful benefit of pirfenidone in patients suffering from IPF.

Thank you for your attention. Dr. Porter will now review the safety of pirfenidone.

DR. PORTER: Let's now turn to a review of the safety experience with pirfenidone. The safety database for pirfenidone, which is relatively large and well-characterized compared to most other orphan

drugs, comprises 1345 unique subjects and patients treated in 15 different clinical trials at doses ranging from 801 to 4806 milligrams per day.

Of these, 770 patients have received the to-be-marketed dose of 2403 milligrams per day in the InterMune Phase 2 and Phase 3 trials. As you just heard from Dr. Bradford, 345 of these patients received this dose in the two InterMune Phase 3 trials. An additional 342 patients, who received either low dose or placebo in the Phase 3 trials, have received 2403 milligrams in the 012 extension study. And finally, 83 patients have received this dose in the ongoing safety study, 002.

In terms of duration of exposure, 436 patients have received at least 12 months of exposure, again, in the InterMune Phase 2 and 3 trials, and 280 patients have received at least 24 months. The smaller cohorts of patients have received longer exposures, again, owing to the fact that the 002 study began in 2003.

So this entire safety database was subjected to a complete analysis, the highlights of which are

contained within your briefing document. For the purposes of this morning's presentation, I will focus primarily on the most robust clinical experience that comes from the two InterMune Phase 3 trials, and I'll supplement that with information from other studies where it's relevant.

So an overview of the combined experience from the two Phase 3 trials is shown here, with the pooled pirfenidone 2403 patients on the left column and the placebo patients on the right column. And as would be expected for a disease such as IPF in clinical trials of 72 weeks' duration, virtually all patients experienced at least one treatment-emergent adverse event, and approximately a third of patients in each treatment group experienced at least one serious adverse event.

Now, a significant proportion of patients in both treatment groups experienced a treatment-emergent adverse event leading to at least a temporary dose modification, and this occurred more frequently in patients treated with pirfenidone than those patients receiving placebo.

This was due, at least in part, to the fact that both Phase 3 protocols contained guidelines for dose modification in the event of certain toxicities, most notably, gastrointestinal events, skin events, or abnormalities in liver function tests.

However, less than 15 percent of patients in the placebo group actually discontinued due to an adverse event, and this occurred in only 6 percent more patients in the pirfenidone group relative to the placebo group. And as you've already heard from Dr. Bradford, on-treatment mortality was lower in patients treated with pirfenidone.

The most common adverse events that occurred more frequently in patients treated with pirfenidone were typically gastrointestinal in nature -- nausea, dyspepsia, and vomiting -- or skin events -- rash and photosensitivity reactions. Dizziness was also more common in pirfenidone patients, 18 percent versus 10 percent in the placebo patients, an observation that's been made in previous clinical trials. So overall, the clinical experience observed in the two Phase 3 trials is consistent with prior clinical

experience.

Idiopathic pulmonary fibrosis reported as an adverse event was actually the most common treatment-emergent adverse event leading to treatment discontinuation, and this occurred in approximately equal proportions in the two treatment groups.

The next most common adverse events leading to treatment discontinuation were rash and nausea, which occurred in 1.4 percent, or five patients each, in the pirfenidone group versus no patients in the placebo group.

Of note, bladder cancer led to treatment discontinuation in .9 percent of pirfenidone patients, or three patients, versus zero in the placebo group. However, the overall incidence of bladder cancer was three versus two, with the two cases in the placebo group not being associated with treatment discontinuation.

The occurrence of any other individual serious or adverse event leading to treatment discontinuation was low, as is shown on this slide. So overall, relatively low rates of treatment

discontinuation relative to the placebo group, and, in general, due to the known side effects associated with pirfenidone.

The occurrence of any individual serious adverse event was relatively low and balanced, in general, between the two treatment groups. There was a small imbalance in patients experiencing serious adverse events of coronary artery disease or chest pain.

However, a thorough analysis of all adverse event terms related to ischemic heart disease revealed no imbalance between the two treatment groups. And the incidence of other individual serious adverse events were less than 1 percent, with no clear imbalances between treatment groups.

As Dr. Bradford has already shown, the incidence of on-treatment death was lower in patients treated with pirfenidone. This is shown graphically here for patients on pirfenidone in blue, and gold in placebo, both for all-cause and IPF-related, as assessed in a blinded fashion by the investigator. Of note, the confidence intervals around the hazard ratio

for IPF-related death exclude one.

Now, prior to unblinding the Phase 3 studies, a number of events and categories of events were designated adverse events of interest. This was based on previous clinical and preclinical observations with pirfenidone, as well as safety considerations in a primarily older patient population with IPF.

After unblinding the studies, this list was refined to the ten categories of events and events listed on this slide, which, again, were then subjected to a thorough safety analysis, the highlights of which are in your briefing document.

For the purposes of this morning's presentation, I will focus on the three categories of events that are most important in informing the benefit-risk analysis of pirfenidone. Those are gastrointestinal events, hepatic events, and photosensitivity reactions and rash. In addition, we're happy to answer questions you may have about other events on this list that I will not cover in the presentation due to time constraints.

Gastrointestinal events were more common in patients treated with pirfenidone. That's shown graphically here for the five most common adverse events. This was particularly true for nausea and dyspepsia, which occurred in approximately 10 to 20 percent more pirfenidone patients than placebo patients.

As is shown on this slide, however, which focuses only on patients treated with pirfenidone, almost all of these events were mild to moderate in severity, or grade 1 or 2 as indicated by the light blue bars, with very few more severe events, grade 3 or 4, occurring as indicated by the dark blue bars. There were only two serious adverse events reported across these five categories of adverse events. In addition, dose modification, which was typically temporary, was required in a minority of cases, and treatment discontinuation was rare.

So overall, gastrointestinal events were more frequent in patients treated with pirfenidone. However, they were typically mild to moderate in severity, required dose modification in a minority of

patients, and rarely led to treatment discontinuation.

Proposed labeling will contain recommendations for pirfenidone to be taken with food to improve tolerability, and for temporary dose modifications if gastrointestinal symptoms persist.

Rash and photosensitivity were also more common in patients treated with pirfenidone. That's shown here, again, graphically. This was particularly true for rash, or events reported as rash, which occurred in approximately 20 percent more patients treated with pirfenidone than placebo.

There does appear to be a significant photosensitivity component to the rash observed with pirfenidone in the Phase 3 studies, and that's shown here, which depicts the number of events per 100 patient exposure years on the Y axis, by month of the year on the X axis, for pirfenidone in blue and placebo in gold.

Though one sees an increased incidence of rash and photosensitivity reactions in the late spring and early summer months of April, May, and June in patients treated with pirfenidone, that's not observed

in patients treated with placebo. Again, this is consistent with previous clinical and preclinical observations, suggesting an association of photosensitivity with pirfenidone.

However, the overall pattern with respect to severity was very similar to that seen with gastrointestinal events, and that's shown here, which, again, focuses only on patients treated with pirfenidone. That is, almost all of these events were mild to moderate in severity, again, as indicated by the light blue, with far fewer more severe events, as indicated by the dark blue. There were only two serious adverse events reported for either rash or photosensitivity.

Again, dose modification, which was typically temporary, was required in a minority of patients, and treatment discontinuation was rare.

So in summary, again, rash and photosensitivity were associated with pirfenidone, typically mild to moderate in severity, and were effectively handled with dose modification in the Phase 3 studies, given the low rates of treatment

discontinuation.

I think it's important to point out that there were no cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylactic reactions, or hospitalizations associated with any skin events in the two Phase 3 studies.

Proposed labeling will contain recommendations for sun protection measures, and, again, for temporary dose modification, if warranted, based on the severity or persistence of skin events.

I'd like to turn now to a discussion of hepatic events. There's one case in the entire safety database meeting the criteria for Hy's law, and that case occurred early in clinical development in the Phase 2 study, SP2, conducted by Shionogi in 2001.

This patient received pirfenidone at a dose of 1800 milligrams per day and developed significant elevations in ALT, AST, and bilirubin on day 56 of therapy. Treatment was discontinued, and this was followed by rapid improvement in liver function tests, which reached normal or near-normal values over the subsequent two weeks.

There have been no other cases clearly meeting the definition for Hy's law, which, I'll remind you, is a concurrent elevation of transaminases and bilirubin in the absence of alkaline phosphatase elevation or alternative etiology. There have been no other cases clearly meeting the definition for Hy's law in either the Shionogi or InterMune clinical development programs, including the long-term extension safety 012 study, nor in the post-marketing experience in Japan since 2008.

There was, however, a small imbalance in transaminase elevations observed in the Phase 3 studies, and those results, based on central laboratory findings, are shown here, again, for the pooled pirfenidone patients in the left column and the placebo patients in the right column.

Fourteen patients or 4.1 percent of patients treated with pirfenidone had an elevation in ALT or AST of at least three times the upper limits of normal, as compared to two patients or .6 percent of patients in the placebo group.

These were typically low-grade elevations,

as there was no imbalance of more severe elevations greater than five times the upper limits of normal. And no patient had a total serum bilirubin greater than two times the upper limits of normal.

There were three liver-related serious adverse events in pirfenidone patients, or .9 percent, versus one, or .3 percent, in the placebo patients. There were no liver-related deaths, and as I mentioned a moment ago, no cases meeting the criteria for Hy's law.

Now, both protocols, as I mentioned earlier, contained guidelines for dose modification in the event of liver function test abnormalities, and 12 patients, or 3.5 percent, of the pirfenidone group had at least a temporary dose modification due to elevations in transaminases. However, only two patients, or .6 percent, actually discontinued due to ALT or AST elevations.

Now, I'd like to give you a better understanding of these 14 pirfenidone patients that had an ALT or AST elevation greater than three times the upper limits of normal, and I'll do that by very

briefly showing you the transaminase patterns for each of these 14 patients.

On this slide, the Y axis depicts ALT or AST value, whichever was most abnormal for the individual patient, expressed as a multiple of the upper limits of normal. The X axis depicts study week, and the dotted line is the transaminase level corresponding to five times the upper limits of normal.

The individual line plots here are for the 11 of 14 patients that had an elevation in transaminases less than five times the upper limits of normal, and the plots depict their profiles up until the point of their elevation. So let's look at what subsequently happened to these 11 patients.

One patient presented at week 60 with severe respiratory failure associated with IPF, and, at that time, had elevation in both transaminases between 3.5 and 4 times the upper limits of normal. Treatment was discontinued in this patient. This patient subsequent died approximately two weeks later due to respiratory failure, with no follow-up laboratory values available.

Two of these patients actually were continued on full dose, as indicated by the green line, with no interruption, had resolution of their transaminase elevations, and were able to continue on full-dose therapy without recurrence of their LFT abnormalities.

The remaining eight patients were placed on a reduced dose of pirfenidone, as indicated here by the light blue lines, in some instances, after a temporary interruption of therapy. And in all eight cases, these patients were able to continue on a reduced dose without worsening of their transaminases elevations.

Three patients experienced elevations in ALT or AST greater than five times the upper limits of normal. And these three patients correspond to the three liver-related serious adverse events that I mentioned on a previous slide.

Two of these patients were able to be placed on a reduced dose of pirfenidone, again indicated by the light blue lines, in both instances, here, after a treatment interruption and normalization of the liver

function test. And both of these patients were able to continue on that reduced dose without recurrence or worsening of their transaminase elevations.

Of note, the patient that presented at approximately week 42 with elevations in serum transaminases, as was briefly described in our briefly document, as well as in FDA's briefing document, was characterized as a patient possibly meeting Hy's law criteria.

I just want to clarify that this patient does not meet Hy's law criteria. They failed to meet two of the three criteria required in FDA's guidance document on drug-induced liver injury. Importantly, this patient had an elevation in alkaline phosphatase 10 times the upper limits of normal, as well as a very close temporal relationship with a 10-day course of Augmentin, which is well recognized to be associated with liver injury.

So while this patient certainly had evidence of liver injury and had elevations in bilirubin values based on local laboratory results, they did not meet the criteria for Hy's law in terms of predictive

value.

Finally, the last patient in this group had treatment permanently discontinued, as indicated by the red line, and LFTs had normalized on follow-up approximately six weeks later.

So in summary, liver function test abnormalities did occur more frequently in patients treated with pirfenidone at a relatively small rate of approximately 4 percent. However, they were generally mild to moderate. And as can be seen from the line plots that I just reviewed, most of these cases occurred within the first six months of therapy. They were reversible in all cases, not associated with clinical sequelae, and, in the Phase 3 studies, were effectively managed with dose modification.

I think the potential for elevations in serum transaminases is an important point, and proposed labeling will contain recommendations for LFT management, including both liver function test monitoring, as well as dose modification, where warranted.

Liver enzymes should be measured prior to

initiation of therapy with pirfenidone, then monthly for the first six months, and every three months thereafter. In addition, it's important that patients be instructed to report symptoms of liver disease promptly to their physicians, such as jaundice or darkening of their urine.

With respect to dose modification for elevations up to five times the upper limits of normal, confounding medications should be discontinued where possible and the patient should be monitored closely. The dose may be maintained at full dose, if clinically appropriate, in the physician's judgment, or reduced or interrupted and then subsequently re-escalated back to full dose, as tolerated, based on liver function test.

Finally, for elevations in transaminase levels greater than five times the upper limits of normal or those associated with significant elevations in bilirubin, treatment should be permanently discontinued.

Let's leave the Phase 3 studies now and briefly touch on relevant safety results from other

clinical trials. The Phase 3 study conducted by Shionogi, the SP3 study, showed a safety profile that's overall consistent with the one I've just described to you from the combined InterMune Phase 3 studies.

The same is true with the long-term safety profile that's been seen to date in the two long-term studies, the 002 study and the 012 extension study. That involves up to about 72 months of follow-up, again, owing to the 002 study having been started in 2003.

The same observation is true for the post-marketing experience in Japan, which consists of a post-marketing study being conducted by Shionogi that's enrolled over 1,400 patients, who are assessed at regular intervals corresponding to the same time frequency that was used in our Phase 3 trials. To date, there's been no new safety signals in those patients during those assessments.

Now, because of the photosensitivity associated with pirfenidone, as well as the potential for elevations in transaminases, we are proposing a

risk evaluation and mitigation strategy for pirfenidone. The goals of the proposed REMS are to encourage informed benefit-risk decisions and the safe and appropriate use of pirfenidone in IPF patients, and to minimize the potential risk of hepatotoxicity and photosensitivity reaction or rash.

The proposed REMS will contain recommendations for liver function monitoring and sun protection measures which would mirror those in the label. And these recommendations would be communicated and reinforced through both a patient medication guide, as well as a health care provider communication plan.

In addition, communication would be facilitated as pirfenidone will be distributed through a closed network via specialty pharmacies, owing to the relatively small number of IPF patients.

So in summary, the overall clinical experience has shown a favorable safety profile for pirfenidone, with a similar incidence of serious adverse events and fewer deaths observed in patients treated with pirfenidone as compared to placebo.

The adverse events are best characterized as primarily manageable tolerability issues, which are mild to moderate in severity in the majority of cases. Gastrointestinal events and photosensitivity and rash are more common in patients treated with pirfenidone. However, they rarely lead to treatment discontinuation.

There's a small imbalance in transaminase elevations observed in the Phase 3 trials. These were readily monitored, reversible, not associated with clinical sequelae, and were effectively managed with dose modification in the Phase 3 studies.

Importantly, there's been a consistent safety profile observed in long-term experience and in post-marketing experience with pirfenidone in Japan.

So in summary, we believe adverse events associated with pirfenidone can be effectively managed through labeling and REMS, and in conjunction with recommendations for sun protection measures, liver function test monitoring, and dose modification, where appropriate, will allow the safe use of pirfenidone in patients with idiopathic pulmonary fibrosis.

I thank you once again for your attention, and I'd like to ask Dr. Noble to discuss the benefit-risk.

DR. NOBLE: Good morning. My name is Paul Noble, from Duke University. From my perspective, as a physician and scientist who has focused his professional career on the care of patients with idiopathic pulmonary fibrosis, working on clinical trials, and trying to find new mechanisms of disease in the laboratory, it's my privilege today to discuss the first body of evidence supporting a favorable benefit-risk ratio for a drug for this terrible disease.

IPF represents an enormous unmet medical need. The prognosis is dismal. The hallmark is unrelenting breathlessness and irreversible loss of lung function. Survival is poor.

From the patient's perspective, which is why we're here today and I look forward to hearing from them, it's devastating. Essentially, their lungs -- they suffocate from their lungs filling up with Jello, and there is no standard of care.

We see approximately 40 patients every week at Duke with idiopathic pulmonary fibrosis. Many of my patients have gone on the internet before they come to see me, and it's a traumatic experience. They feel they have no hope. My best days are always when someone comes to me with a diagnosis of IPF and I find out they don't have it, because that's the best way to treat it.

The medications that we've used -- corticosteroids, azathioprine -- are of unproven benefit and have significant toxicities. There have been challenges to bringing drugs to IPF patients. It's a complex and poorly understood disease. The nature of disease progression is variable. It's a heterogeneous disease. Progression is inevitable, but it's unpredictable. Everybody will get worse, but we don't know exactly when.

There's also limited experience to guide trial design. Sadly, just this past week, we learned that a clinical trial with over 600 IPF patients for over four years, testing an endothelin receptor antagonist, failed to meet its primary endpoint. It's

in this context that positive Phase 3 trials represent pioneering work.

There are several lines of evidence to suggest that there's a clinical benefit of pirfenidone on lung function in IPF. First, 004 and 006 are well-conducted studies. Excellent patient retention. Minimal missing data. Rigorous analysis.

004 showed a clear and durable impact on the decline in FVC, improved progression-free survival, and, importantly, reduced the catastrophic categorical decline in FVC of greater than 10 percent. I use that term "catastrophic" because I just want to remind you that the scale of lung function is not 0 to 100. It's more like 40 to 80.

It's unusual for an IPF patient to have an FVC greater than 80 percent, because it's normal. And as we heard from Dr. du Bois, when your FVC gets to 40 percent, unfortunately, you're rarely alive. So in that context, a 10 percent change is a major loss in lung function. And when you're starting from 60 percent, you don't have a lot of reserve.

006 did not give us identical results.

There were similar effects on FVC through 48 weeks of study. This was disappointing, but given the variable rate of decline in FVC, I didn't find it enormously surprising. The recently published Shionogi Phase 3 trial showed a similar effect on vital capacity and progression-free survival through 52 weeks. I find this reassuring.

A major point of discussion today is whether the observed effect on percent predicted FVC is clinically meaningful. Let me tell you why I think it is.

First, the primary efficacy analysis demonstrated a clear and convincing treatment effect. Now, this result reflects the treatment effect across the entire IPF population. In order to better understand the impact on individual patients, it is best to look at the categorical changes in FVC.

What we found was that pirfenidone significantly reduced the number of patients who experienced the most substantial loss of lung function, and this was about a third of the patients. Pirfenidone also increased the number of patients

whose lung function did not decline.

FVC matters in IPF. It's not enormously helpful in asthma, COPD, or pulmonary hypertension, because the physiology is difference. Forced vital capacity is our best measure of declining lung function in IPF. Declines in FVC predict mortality and irreversible morbidity.

A drug for IPF that does two things -- puts a brake on the rate of decline in lung function across the whole study population, and substantially reduces the percentage of patients that suffer a major loss of lung function for a year or more -- is a significant step forward and likely to provide meaningful clinical benefit.

We also observed a consistent treatment effect over several different outcome measures. These data help me, because I can inform my patient what pirfenidone might do for them over the next year and a half. What we're looking at here is a risk estimate versus different outcomes. A risk estimate of 0.7 means the patient is 30 percent less likely to have a major loss in lung function of greater than

10 percent.

We also saw a risk estimate of .74, or a 26 percent reduction, in the risk of losing 50 meters of walk distance. Now, that 50 meters number was arrived at in a post hoc analysis, where we looked at the over 1,000-patient database from the failed Actimmune trials and found that patients that lost 50 meters had a fourfold greater risk of mortality, and then we applied that to this data set.

We also observed a 26 percent reduction in the risk of disease progression. And finally, although the trials were not powered for mortality, when we looked at overall survival by intent-to-treat analysis, we found a 23 percent reduction in the risk of death that favored pirfenidone.

Now, let's turn to safety. The safety profile is derived not only from the experience in the trials you've heard about today, but also the experience in Japan, where the drug is available to patients with idiopathic pulmonary fibrosis.

The primary issues were tolerability and not morbidity. The common adverse events -- GI symptoms

and photosensitivity rash -- were seen in the previous studies, and few led to treatment discontinuations. Aminotransferase elevations were observed in a small proportion of patients. But when the dose was reduced or the medication was discontinued, they completely returned to normal.

I also want to remind you that IPF patients frequently see their pulmonologists, and we have experience with medications like corticosteroids, azathioprine, that have more severe side effects.

In conclusion, there are about 100,000 patients currently suffering from IPF in the United States. It's a fatal disease with no treatment options. The totality of the clinical data demonstrate a clear treatment effect.

Pirfenidone did not cure IPF. It did not make patients better. But as a pulmonologist who knows idiopathic pulmonary fibrosis, I firmly believe that preventing loss of lung function in an irreversible disease is clinically meaningful.

Importantly, the risks are manageable and acceptable. When we look at the whole landscape for

idiopathic pulmonary fibrosis, everything you'll see and hear today -- the unmet medical need, the safety and efficacy of pirfenidone -- the conclusion is that pirfenidone is an important first step in IPF treatment, the first drug to have a favorable benefit-risk profile.

As a pulmonologist, I would like to be able to offer my patients with idiopathic pulmonary fibrosis pirfenidone. Thank you.

DR. CALHOUN: Okay. Thank you. The committee appreciates you keeping your presentation on time.

At this point, we have an opportunity for committee members to address questions of clarification for the sponsor. And maybe I'll take chairman's prerogative and ask you one.

In your data slides in which you evaluated the proportion of people who had a 10 percent change in vital capacity, your data slide CE-15, you show the data for the 004 study. And later on, 36, you show the data for the pooled study.

Do you have a comparable analysis for the

006, or did I just miss it? I'm sorry.

DR. PORTER: Thank you. I'll ask Dr. Bradford to share that data with you.

DR. BRADFORD: Could I have FVC-54, please? We do have a similar analysis. It's not based on the two categories, but rather the full five categories, which I'll share with you now. Slide up.

As I mentioned in the presentation, the pre-specified analysis was really a five-level analysis of categorical change in FVC. Here's the full five levels in the 006 study.

And at the week 72 time point, as you can see, and consistent with the difference in treatment group means, there's very little activity evident in the drug, a p-value of .440. The point estimates for each of these categories tends to favor pirfenidone over placebo, but there's really no meaningful treatment effect whatsoever here at week 72.

DR. CALHOUN: And do you have data for the intermediate time points in a distribution like this? On your group mean data, there were differences in the 006.

DR. BRADFORD: Yes. We don't actually have this full data at the intermediate time points. I can show you some data on the dichotomization at decrements of 10 percent, if you'd like.

DR. CALHOUN: Okay. Thank you.

DR. BRADFORD: FVC-57, please. We have tended to focus on the 10 percent decrement, both given the pre-specification and the progression-free survival analysis, and have all the focus on that particular decrement in the medical literature. Slide up, please.

So here are the results from 004, looking at proportion of patients with 10 percent decrements in forced vital capacity by study assessment time point. And as you can see, as we've seen in other analyses in 004, the treatment effect does emerge relatively early and increases in magnitude, and persists out to week 72.

DR. CALHOUN: Okay. Thank you.

Dr. Hendeles?

DR. HENDELES: I have three questions for clarification.

First, did you measure pirfenidone serum concentrations during either of the pivotal studies? And if so, was there a relationship between either efficacy or adverse effects?

The second question is: How did you quantitate adherence?

And the third is: You mentioned that there was a dose response, and from what I've read, it appeared that there wasn't. And I'm wondering how you arrived at that statement.

DR. PORTER: So three questions, if I heard them correctly. Serum concentrations in the Phase 3 study and any PK/PD-type relationships. The second was how did we quantify adherence, and the third was comment on dose response, if that's correct.

Let me start with the second one, if I might, with respect to how did we quantitate adherence. We did have subject diaries that recorded what medications, what capsules they took that were returned and checked and recorded. So we did record that information that way.

With respect to dose response, as

Dr. Bradford pointed out, we did include an underpowered low-dose group, and it was mainly for informing, not for statistical comparison. So the comments about dose response are that, basically, where there was evidence of a treatment effect on the 2403 group, in general, the intermediate dose group -- or the lower dose group was intermediate, in effect.

From a safety standpoint, I would comment that there were multiple episodes of a dose response with respect to safety, where the occurrence of GI events, for example, were intermediate with respect to the high-dose group.

Finally, returning to your first question, we did measure pirfenidone's serum levels in a subset, a PK subset of patients in the 004 study. And with respect to relationships, I'll ask Dr. Chris Rubino to address that question.

DR. RUBINO: Thank you, Dr. Porter. My name's Chris Rubino. I'm with the Ordway Research Institute, and we've been consulting with InterMune since 2004 on the clinical pharmacology of pirfenidone.

We did conduct extensive PK/PD analyses on those 88 subjects, or patients, from the 004 study that we had. We used multi-variable statistical models to try to define the relationships between exposure and response, and also including other variables that might influence response.

What we found were some weak relationships, overall. There were no strong relationships when you looked at multi-variable models. However, those relationships did support the dose response analyses in that the patients at the highest dose level would be expected to be in the range of concentrations or exposures that were associated with better efficacy.

Also, we did them for safety, as well, and saw that they would also be more likely for photosensitivity at the higher dose. So there was a differentiation when you looked at it from an exposure-response relationship, as well.

DR. CALHOUN: Dr. Honsinger?

DR. HONSINGER: I also have three questions, the easy one first.

Were patients in the 004 and the 006, were

any of those the same patients? Were these totally different population groups?

The second question: Sure, it looks like 2400 milligrams is better than 1800 milligrams. You must have tried higher dosages. You must have seen more toxicity or lack of benefit or something to choose the 2400 rather than a higher dose. So why did you not do a higher dose study?

And the third question, of course, is: We have a drug that looks like it gives some very modest benefit to a few of the patients who take it. There must have been a search for inflammatory markers or something else to tell which patients were going to have benefit.

Was there any search for inflammatory markers -- CRP, interleukins, angiotensin-converting enzyme, anything we might have seen that was an inflammatory marker that might have shown a benefit?

DR. PORTER: Thank you. I think I got all three questions, so I won't repeat them. Correct me if I miss them, however.

With respect to your first question, these

were two completely independent patient populations. These studies were done at different sites, different patients.

With respect to your second question, I think, as Dr. Bradford pointed out, the dose of 2403 was a weight-normalized dose based on what had been seen in the Shionogi SP2 study, which, at the time we designed our clinical trial, was the only real data available in terms of a treatment effect of pirfenidone.

We do have data from shorter-term Phase 1 studies in both healthy subjects and, in some instances, patients such as with hepatic impairment, where we've explored higher doses. Those are not efficacy studies, of course.

One does see greater adverse events, particularly around gastrointestinal intolerance. So it was primarily based on the available data that we had, but the higher doses are associated with more intolerance.

Finally, with respect to your last question, we did draw serum samples from patients in the Phase 3

trials. We have not yet done the analysis that you mentioned in terms of looking for biomarkers. That is something we plan in the future in working with our steering committee, but we've not done that to date.

With respect to other analyses in terms of identifying patient characteristics, a subset of patient characteristics that respond, we have not been able to find any.

DR. CALHOUN: Dr. Platts-Mills?

DR. PLATTS-MILLS: Thank you. Apologies for turning my back to you. It reminds me of an Ionesco play where people turn away from the people they're talking to.

[Laughter.]

DR. PLATTS-MILLS: I have three questions.

The first is: How much data do you have about the consistency of the disease? In one of the Japanese trials, there's this extraordinary difference between an 1800-milligram dose and a 1200-milligram dose; that is, the 1200 doesn't, which is a curious dose response.

Do you know about culture of the lungs? Do

you know about biopsy of the lungs? And do you know about any suggestion that there's a difference between the disease in Japan and the United States?

The second question: Is exercise part of the treatment of IPF? Exercise is part of the treatment of almost all chronic lung diseases, but I don't know that for IPF and you don't mention it anywhere in your things. Is there improved compliance with exercise on the drug?

The third question is: In all of the studies where there's been a rise in liver enzymes, are there any symptoms that the patient presented, any of the GI symptoms, that actually signal that that is happening? Because that's always been a problem with any drug that raises liver enzymes, that, in general, we don't get a warning until you do the blood test.

Thank you.

DR. PORTER: I'm going to take a shot that I got all three again without repeating them, but please, if I missed them. Let me start with the last one first, with respect to symptoms.

You point out an important point, because

this is a drug that's associated with gastrointestinal symptoms that have some overlap with symptoms that might be associated with liver disease. In general, as you saw in the presentation, most of the elevations were low-grade and were typically caught on monitoring prior to being what were clearly liver-associated symptoms.

In some of the more -- greater than five times the upper limits or more, there were some symptoms that might have been associated. Difficult to say. But again, because no patient had elevation in bilirubin, that was certainly no jaundice or darkening of urine that was found.

With respect to your first question about the heterogeneity of the disease and anything from biopsy, I'm going to make an initial statement on that and then I'm going to ask Dr. du Bois to comment. And I'm also going to ask Dr. du Bois to comment on your second question about treatment -- exercise for treatment of this disease.

In general, while the disease is clinically heterogeneous, the diagnosis is pretty clear from a

histological standpoint. And as far as we know, there are no differences in patients in Japan or in the United States in terms of the disease.

So I'll ask Dr. du Bois to comment further on that, as well as on exercise as a treatment.

DR. DU BOIS: Thank you. Obviously, this is a really crucial point, and we wondered long and hard if there were perhaps phenotypic differences between the Japanese and our population.

By chance, I was just in Japan in January and had lots of conversations with the doctors over there, and we've also exchanged biopsies historically. My belief is that it is the same disease. That does not mean that there are not heterogeneities within the disease. I suspect there probably are, but we're not yet quite smart enough to figure out what they are, and certainly we can't define them on biopsy.

Physical therapy, it drives us crazy. We've been trying to develop physical therapy programs, certainly in the United Kingdom when I was working there and in Europe, and they're really in their infancy. And while I would agree with your

implication that these would be very beneficial to these patients, there are very little data out there in support. There's a little bit, but not very much.

Thank you.

DR. CALHOUN: Dr. Foggs?

DR. FOGGS: Thank you. I have three questions, as well. I'd like to know whether or not there's any evidence that pirfenidone has any therapeutic effect on other interstitial lung diseases, especially as it relates to percent change in the FVC.

In addition, with regards to the discrepancy noted with the reaching of the primary endpoint of percent change in FVC not being accomplished for the 006 study, on panel CE-13, as well as on panel CE-22, looking at the high-resolution CT scanning constituting definite diagnosis of IPF, do you have any explanation for the discrepancy of 95 percent of the patients in the 004 study having H- or CT-definite IPF diagnosis versus 88 percent in the 006 study? And if so, do you think that may have some explanation for the 006 study not reaching the therapeutic endpoint as

it relates to delta FVC change?

Lastly, at week 72, do you have any correlating data with regards to health-related quality of life, even in the 004 study, where the statistical significance was met, but also in the 006 study and the pooled data?

DR. PORTER: Thank you. I think this time I will repeat your questions just to be certain.

The first question, I think, was: Do we have any effects on -- in other diseases, perhaps, of pirfenidone on other interstitial or lung disease? The second was as it related to the difference in 004 and 006 around definite IPF on HRCT. And I think the third was around correlations between week 72 outcomes and quality of life in the studies.

Let me answer your first question first. I'm going to ask Dr. Bradford to address your second two questions.

With respect to your first question, there have been no other rigorous clinical trials of this nature with pirfenidone in other diseases. Certainly, in a variety of animal models, there's evidence for

anti-fibrotic activity in the lung. And there have been some small studies, but certainly nothing that would give any credible information, really, in other diseases.

The sole exception has been Hermansky-Pudlak. It's a very rare disease. There have been a couple of studies in that disease that suggest some effect in terms of anti-fibrotic effects.

So I'll ask Dr. Bradford to address your second and third questions.

DR. BRADFORD: Let me start with your second question about the HRCTs. There is a small imbalance across the studies with respect to definite IPF on HRCT. We don't believe that has any effect on the different outcomes at week 72 in the primary endpoint analysis.

I'll remind you that if patients did not have definite IPF on the HRCT, they were required to have a confirmatory lung -- surgical lung biopsy. And so, really, there's not a lot of uncertainty about the diagnostic outcome here. We did not look at different radiographic phenotypes, if you will. We've not done

those analyses to date.

With respect to your second question, we have looked at quality of life-type issues, specifically at dyspnea. And the HRQOL was an exploratory endpoint in the study. There's no activity whatsoever on the HRQOL.

Dyspnea, the endpoint was not met -- it was a secondary endpoint -- in either study, quantified by the UCSD SOBQ instrument, which is, unfortunately, not a validated instrument in this disease process. However, going back and looking at the dyspnea in a post hoc way, there does appear to be some separation in the treatment group curves, particularly when one focuses on patients that have very significant increases in the level of dyspnea.

Could I have SS-89, please? Slide up, please. Just to share this, I'll caution you, this is a post hoc analysis, but it gets at the issue of quality of life and PRLS symptoms, et cetera.

So looking at the SOBQ scores, again, a measure of dyspnea dichotomized at 25, what we do see here is a suggestion -- and it's only a suggestion --

that the pirfenidone patients, a fewer proportion of those experience large increases in their dyspnea relative to placebo.

But really, there's no strong evidence with respect to dyspnea, health status measured by St. George Respiratory Questionnaire, or quality of life measured by the HRQOL.

DR. CALHOUN: Okay. At this time, I'm going to take my turn and not assert chairman's prerogative. I've got questions around two issues.

The first relates to the differences between study 004 and 006. And as I look at the data, and I'm sure you've looked at it very much more carefully than I've been able to, but it appears to me as though the treatment effect, or the change in lung function in treated patients in those two studies, is not very different. But what is different is that the folks in the placebo group in the 004 study deteriorated to a greater degree than did those in the 006 study.

So that, obviously, raises questions about the patient population. 004, as I understand it, was a U.S. study. 006 was an international study. And so

can you talk a little bit about the kinds of patients who were recruited in the international study, whether you'd looked for a country effect in your data set, and although I understand the numbers may be small, whether you looked at your data set in study 006 to see whether the U.S. patients who were recruited in 006 looked like those in study 004, or whether they looked like the study 006?

I'll deal with the second question -- that was a complex question, so I'll let you deal with that one first.

DR. PORTER: Okay. Thank you. Let me just address part of that question, then I'll ask Dr. Bradford to expand on some of it. I do want to just clarify one thing and make sure everyone's aware of the fact that both studies were multinational studies. There was a difference in the percentage of patients ex-U.S. that were enrolled in the two studies, but they both were multinational studies.

So we have, as you correctly pointed out, spent an enormous amount of time looking at these issues between the two studies. You are correct, as

well, that when one looks at the pirfenidone groups in the two studies in terms of decline in FVC, they're very identical curves. When one looks at the placebo groups, they're different in the latter half of the study, as you pointed out.

So I'll ask Dr. Bradford to go into a little more detail on that, and also your question around the United States subset.

DR. BRADFORD: Let me start with FVC-9, please. Slide up, please. So just to graphically show the point that's being made here, this is primary endpoint changes based on mean change from baseline over the duration of the study period, comparing the 004 and the 006 studies. Here's the results in the pirfenidone groups. As one can see, they're essentially superimposable on the two studies.

Here are the results for the placebo group. And what we see, beginning around week 24, there is really a clear attenuation in the rate of decline in the placebo group in the 006 study. And the question, obviously, is why. Let me address your next question as part of the answer to that.

Could I have BL-2, please? This was a large multinational trial -- slide up, please -- where we had, I believe, around 12 countries participating. As one can see here on the slide, which summarizes the clinical sites, the number of patients enrolled by country, the vast majority of the patients were enrolled at U.S.-based sites.

There were a number of sites outside the U.S., both in Europe, Mexico, Australia, et cetera. However, they contributed a fairly small number of patients. This unfortunately has prevented us from being able to look at specific country effects. And for that matter, no single site in the study enrolled more than 8 percent of patients, so we've not been able to look at site effects, per se, either, owing to the way that the enrollment went.

To finish my response to your question, could I have slide FVC-26, please? We have, obviously, looked long and hard for explanations on the differences in the week 72 outcomes across the two pivotal studies, conducted literally hundreds of analyses, and had a large number of experts helping us

in this exercise. And the bottom line is we don't know the answer.

But to share a little more data that kind of gives an example of what we looked at -- slide up, please -- here are the subgroup analyses that we've conducted looking at week 72 FVC change across the two pivotal studies. So these are pooled analyses.

I think the first point is just the pattern. Obviously, the vast majority of these estimates -- actually, all but one -- go in favor of pirfenidone over placebo. But I think once one drills down in this and looks in the data quite a bit, there's no evidence of a compelling effect modifier that's also imbalanced across the two studies that provides a specific answer to the issue about the differences in the primary endpoint at week 72.

Based on all these analyses, we've come really to the diagnosis of exclusion, if you will, is that this is likely just reflective of the intrinsic variability in rates of FVC decline in these patients.

DR. CALHOUN: So my second question actually went directly to this point. That is, have you looked

at demographic predictors of response to therapy? And obviously, you have.

Okay. Next, Dr. Knoell.

DR. KNOELL: Thank you. Most of my questions have been addressed, but I just have one related to your ongoing program with how to handle dosing in specific patients, in particular, compromised renal or liver function. And then related to that, knowing that the drug is a substrate for a variety of CYP450 enzymes, what your future intentions are to deal with that, knowing that many of these patients will be on regimens of multiple medications.

DR. PORTER: With respect to handling dosing in the ongoing studies, at least for labeling, anyway, we'll propose dose modification guidelines, and I mentioned that, in terms of specific tolerability issues.

We have studied the drug in hepatically-impaired patients, as well as renally-impaired patients, and I'll ask Dr. Rubino to comment on that. And we'll come back to the question on CYP, perhaps, after he makes a brief comment on that.

DR. PORTER: Well, let me handle the renal function first. There was a renal impairment study that was done, and the effect of renal impairment really only happens with 5-carboxy, the metabolite. So there's no effect on the pirfenidone concentrations in patients with renal impairment.

So at this point, the recommendations for the labeling are no change in mild to moderate renal impairment, use with caution in severe, and there's no data in patients on dialysis, so essentially avoid use in those patients.

As far as hepatic impairment, it's a bit of a muddier picture in terms of dose modification. There was an hepatic impairment study done. The patients with moderate hepatic impairment, Child Class B, had lower clearance or higher AUCs of pirfenidone, but it wasn't consistent.

Can I have the next slide after this?

Slide up, please.

It's not a large study, as hepatic impairments are often small. This was a Phase 1 study, a group of 12 -- if I remember correctly -- 12

patients with moderate hepatic impairment and 12 with normal hepatic function. And on a mean basis, it was statistically significant. Higher exposures pirfenidone AUC is what you're looking at here.

But the overlap was significant. And thus, the recommendations for labeling would be to use with caution in these patients due to the possibility for increased exposure, but not to dose modify a priori, because of the potential of under-dosing those patients.

So that, I believe, should answer the question related to hepatic impairment.

DR. PORTER: I may call you back in just a second, so maybe you want to hang close by.

With respect to your question around CYP interactions, from an in vitro standpoint, in terms of pirfenidone inhibiting or inducing CYP isoenzymes, there's really no evidence that that's an issue.

With respect to interactions with other drugs, we did conduct a drug interaction study with fluvoxamine, which, as you know, is a strong inhibitor both of CYP1A2 and other CYPs, as well. And that

study did show a significant effect on pirfenidone exposure and, for that reason, the proposed labeling contraindicates administration with fluvoxamine.

However, pirfenidone is metabolized by 1A2, as well as multiple other CYPs. And when we looked in the Phase 3 study for drug interactions with other CYP1A2 drugs, there's no evidence of any problem there, either from an exposure standpoint or from a safety standpoint.

So the proposed labeling will just recommend caution in use with the strong CYP1A2 inhibitors.

DR. CALHOUN: Dr. Hendeles?

DR. HENDELES: What was the evidence that titrating the dose at the beginning significantly reduced GI side effects?

DR. PORTER: That comes from early clinical experiments, primarily done by investigators in the study in Japan, which had employed that dose titration as well. That appears to reduce the incidence of gastrointestinal tolerance.

We've studied that in our Phase 1 studies, but not directly comparing non-dose titration. It's

just basically been something we've employed because it's appeared to work throughout the clinical development program.

DR. CALHOUN: Dr. Terry?

DR. TERRY: I noticed in the reading material that we were provided that a significant number of these patients had their diagnosis made a year or more before they entered the study. Did you collect any of the pulmonary function tests, which I assume were done at the time of their diagnosis?

And my second question is: Do you know how many of these individuals had been on prior immunosuppressive therapy prior to entering your study and had any of them responded to it?

DR. PORTER: With respect to your first question, certainly, not for patients diagnosed more than one year prior to entry into the study. We do not have the pulmonary function test data from those individual patients.

With respect to your second question, let me confer with Dr. Bradford.

[Pause.]

DR. PORTER: I'll let Dr. Bradford comment.

DR. BRADFORD: We don't have systemic quality data on how patients were previously treated. I will as Dr. du Bois, perhaps, to just comment, in his experience, what he would suspect was happening with these patients.

DR. DU BOIS: There really is no evidence that any of the therapy has any efficacies, although I would agree with Dr. Bradford that we have no hard data to answer that question absolutely specifically. But these patients, being enrolled in the study, were likely, at best, stable or deteriorating. But I say, again, I think there's very little data that would support the efficacy of anything that these patients might have been receiving.

DR. TERRY: I actually wasn't looking for evidence of absence of efficacy. I was looking for evidence of a wrong diagnosis --

DR. DU BOIS: I see.

DR. TERRY: -- or if some of them had responded to an immunosuppressive agent, that would raise the question of the diagnosis.

DR. DU BOIS: Right. Sorry, I misinterpreted. I think that the CT and biopsy criteria that Dr. Bradford has set out make it very unlikely that there was significant, if any, errors in diagnosis.

DR. CALHOUN: Dr. Krishnan?

DR. PORTER: If I could just add one comment to that. There was an inclusion/exclusion criteria in the study which prevented patients that had had evidence of improvement in the prior year from being enrolled. So that at least helps possibly address your issue.

DR. CALHOUN: Thank you. Dr. Krishnan?

DR. KRISHNAN: Thank you. I have two questions on the primary endpoint FVC.

The first one is that given what we've heard about the substantial intra-patient variability, I wonder if you could comment on why group means were used as the primary endpoint rather than the categorical endpoint of number of people or proportion of people with 10 percent or more change. That's the first question.

The second question relates to the absolute difference between the treatment groups, both in 004 and 006. In 004, there was a 4.4 percent difference in change in the FVC, 006 .6 percent, and the pooled effect was 2.5 percent favoring the treatment.

Given some of the information you had projected before about how differences in change in the FVC are related to mortality, those differences seem to be larger effects, such as 5 to 10 percent differences in change. And I wonder if you could comment on what you think is the clinically meaningful benefit of a 2.5 percent pooled difference in change.

DR. PORTER: Thank you. I think you've asked one of the most fundamental questions in understanding the results of these two trials, particularly as it relates to around the primary analysis versus how one looks at the estimation of the magnitude of effect.

I'm actually going to ask Dr. Koch to answer this question, because I think it's a key one.

DR. KOCH: Gary Koch, Biostatistics Department, University of North Carolina. I'd first

indicate that all of my activity on behalf of InterMune is through a cooperative agreement with the University of North Carolina. That agreement supports part of my salary. It supports travel expenses, as well.

I have had collaborative interactions with InterMune throughout the planning, statistically, of the 004 and 006 studies. And so much of the analysis plan that these studies had had my input to it.

The primary analysis at week 72 was very definitely not a comparison of means. Means were provided descriptively in a supportive analysis. As you heard in the core presentation, the primary method of analysis was a rank analysis of covariance.

One used ranks because of asymmetries in the distribution of the change in FVC. One also used ranks because of the difficulties with respect to the patients who died. It's very problematic to assign a numeric value to the patients who died. But it is straightforward to regard them as having the worst outcome, and so they then got the worst ranks. And that again is another reason why the rank analysis was

used.

As you heard, these studies were very high-quality studies in the sense that patients who discontinued treatment had continued follow-up so that the endpoint could have additional follow-up and monitoring. So the numbers of patients who actually had missing data on the endpoint were very minimal.

Because a rank analysis of covariance does not give convenient descriptive statistics, I strongly recommended to the sponsor to have the categorized endpoint. And if one can put up FVC-53, we can revisit this description.

This gives you the preplanned categorized distribution of the change in FVC. The patients who died are among the patients who had the worst outcome, so they are included with those who had a 20 percent decrease, or worse. Another categorization were those whose decrease was 10 to 20 percent.

A rank analysis of covariance was essentially done on this categorization. This categorization was also analyzed on the rank scale, and also provided p-values comparable to what the

primary analysis provided.

Through this analysis, one gets a direct interpretation of what the rank analysis of covariance primary analysis indicated as a significant result, and as the significance here reinforced. And one can see in these distributions that there definitely are fewer patients in the two worst categories, the less than 20 percent decrease and the 10 to 20 percent decrease, than in the placebo group, where there were substantially more patients in those categories.

If we go back to the core slide, which was CE-15, the sponsor provided to you a simple summary of the left-hand side and the right-hand side of that five-point distribution that was very fundamental to the planning of these studies, so that one would have a clinically interpretable result that came from the rank ANCOVA.

That clinically interpretable result is through the substantially smaller number of patients with a greater than or equal to 10 percent decline, as well as somewhat more patients who had essentially no decline at all. So the pirfenidone group had

relatively more people with the favorable outcome, while having substantially fewer people with the unfavorable outcome.

This is the way to interpret the differences between the groups on this primary endpoint. A difference in means has no utility at all. It's a population measure, and it's particularly problematic here because there are deaths and one really cannot assign a value of the change in FVC to the deaths in a meaningful way.

The sponsor tried to do that in some of the descriptive analyses they provided in their briefing book, as well as in their submission to the agency, but these analyses are inherently problematic compared to simply looking at the categorized change.

DR. KRISHNAN: If I could follow-up with that, then given the inherent limitations of group means when you have folks who can't contribute data because of some adverse outcome, could you comment again on the selection of the primary endpoint and the analyses, and why such a presentation didn't include the one shown here on this slide as the primary way in

which to represent treatment benefit?

DR. KOCH: Well, again, the primary analysis was a rank ANCOVA. So it addressed the change in FVC as the change was observed without producing an initial categorization. It simply worked with change in FVC as it was, while assigning the worst ranks to the deaths.

Then to reinforce this analysis, the five categories were used. The five categories were not presented in the core presentation, because that particular slide, if we want to put it back up again, which I believe was FVC-53, is somewhat more difficult to interpret, because what you have to do is to simply add the two yellow bars on the left-hand side and calculate 35 percent, and add the two blue bars on the left-hand side to get 20 percent, to see what the shift is going on there, and then do a similar thing on the right-hand side.

So to make the presentation more straightforward, the core presentation simply provided a summary of the left side, the treatment difference, a summary for the right side. But all of this came

from this preplanned reinforcing analysis to the original rank ANCOVA that dealt with the rank of FVC change as it was.

This is simply a more direct summary of that information. These two criteria are really interchangeable with one another. They were analyzed in exactly the same way.

DR. CALHOUN: Dr. Hubbard?

DR. HUBBARD: Yes. Thank you. I had a couple questions.

First of all, with regard to adverse events, this was a 72-month [sic] trial in patients who were over the age of 60 years, for the most part, and you're treating them with an anti-inflammatory drug, as I understand it. And I'm a little bit surprised that I saw no information about infections as adverse events in any of the data. Can you comment on how infections might have been captured, and if it's true that there were little or no infections within the trial?

And the second question I have is with regard to patient and physician understanding or

appreciation of improvement with therapy. One of the things that we used to do in clinical trials was patient global assessments and physician global assessments of therapy. And I wonder if those were captured in this trial, and if they showed any impact that was appreciable to either the patient or the physician with the impact of therapy in the trial.

DR. PORTER: Thank you. With respect to your first question, just let me reiterate that it was a 72-week trial. So it was not 72 months. I just wanted to make sure there was no confusion around that.

You didn't see data on infections, because there was absolutely no indication of an imbalance with infections. We certainly did collect all adverse events, and they were balanced across infections in general.

With respect to your second question, Dr. Bradford mentioned that we did collect some questionnaire-type data with respect to the HRQOL and other measures. We did not collect, in addition to that, the global assessments from -- certainly not

from the clinicians. We don't have that data.

DR. CALHOUN: Dr. Platts-Mills?

DR. PLATTS-MILLS: Thank you. You mentioned that there was a consistency of the relationship between falling FVC and death. And so the question is, were there any major discrepancies between that? That is, had all the patients who you thought had died of IPF had a significant decline, or were there major discrepancies?

Secondly, some minor points. What was N for those patients who enrolled with an FVC greater than 80 percent? Because that was one of the questions. If you treated milder, in some sense, patients, would they do better? And yet it actually appeared the opposite. Or was the N for that group too low to be meaningful?

You mentioned smokers, but I don't remember anyone -- in discussing one of the side effects, you were looking at smokers and nonsmokers. But I don't remember seeing how many patients were smokers in the initial presentations.

Thank you.

DR. PORTER: Thank you. I'm going to ask Dr. Bradford to address these questions. But can I ask you just to clarify exactly the second question around the 80 percent? I want to make sure we understand it.

DR. PLATTS-MILLS: You showed data for patients who were enrolled who had an FVC greater than 80 percent, and less than 80 percent to something else in another group. And it was only the patients who had greater than 80 percent who didn't favor the drug.

So the question is: What is N for that group?

DR. PORTER: Okay. Thank you. Now I understand. I'll ask Dr. Bradford to address your questions.

DR. BRADFORD: Slide up. First, to answer your first question about the relationship between FVC change and mortality, we have looked at this in an analogous fashion to what's reported in much of the literature, namely, looking at changes over, say, a 24-week period of time and subsequent risk of mortality.

Here you see that data in the placebo patients, so that the relationship is not confounded by treatment. And what we see here is, looking at the proportion of patients that died based on FVC declined status at week 24, that the patients that dropped their FVCs by 10 percent or more, 18 percent of those died versus 6 percent of those that did not. These are small numbers, obviously, but very consistent with what's been widely reported in the literature.

With respect to your second question about proportion of patients with FVC greater than 50 percent at baseline -- could we have FVC-26? Slide up, please. Slide up, please. I can't specifically tell you the N. That's something we'll certainly look up and be able to provide to you, perhaps after the lunch break there.

But looking at this particular issue, here's the subgroup analysis I showed just a few moment ago, based on the pooled data in 004 and 006. And what one sees under baseline severity of FVC change there, if you look at the greater than 80 percent, it's actually the only point estimate that goes in favor of placebo

over pirfenidone.

We actually see this in the subgroup analyses in both the 004 and 006 studies, suggesting that it is consistent, that there's less effect in patients with more preserved lung function.

DR. CALHOUN: Okay. We're going to take two more questions. There are other folks in the queue, and we'll have time after the -- oh, yeah. That's right. Thank you for reminding us.

DR. BRADFORD: Is that BL-3, please? Slide up, please. We do have data on smoking that we can provide you with now. Here's a summary of the baseline characteristics in the two pivotal studies. You can see, about halfway down, current or former smokers. So roughly 70 percent in the 004 study and a little bit below that in 006 study, 66, 63 percent.

DR. CALHOUN: Okay. Thank you. So we're going to take two more quick questions. We have other questions on the horizon, and we'll deal with those in our later time for discussion this afternoon.

Next is Mr. Mullins.

MR. MULLINS: My question is on the nature

of the trials, the clinical trials, 004 and 006. My concern is about the size of the patient or the subject population. The total, the cumulative total, of trials 004 and 006 were 779. Could you speak to the size of that patient population and how that affected your analyses and your ability to make clinically and statistically sound judgments?

And my second question is, could you speak -- there seem to be indications that pirfenidone seems to behave as a carcinogen. Would you speak to your studies, the animal studies and the occurrence of -- and the behavior of pirfenidone as a carcinogen?

Thank you.

DR. PORTER: Thank you. With respect to your first question, you're correct, a total of 779 patients between these two trials. Individually, as clinical trials, these are relatively large trials for IPF, which is a difficult disease to study and recruit for. Certainly, with respect to inferences, we believe and designed these studies to be of adequate size on the endpoint, the primary endpoint, that we chose.

The studies were underpowered, as we've discussed on mortality. And at the time we designed them, we had no data upon which to know how to power for secondary endpoints. But in terms of drawing conclusions from these studies, we certainly believe these are robust experience in this disease.

With respect to your second question, just to make sure I clarify, I believe you're referring to some pre-clinical observations. Is that correct? Could you just clarify exactly which ones you're referring to?

MR. MULLINS: Indications of animal studies. I'm not sure which ones, but there were animal studies done that had indications of high levels of toxicity and pirfenidone behaving as a tumerigenic.

DR. PORTER: Okay. Thank you. Let me review with you briefly, then, what I suspect you're referring to, which are two specific types of tumors that were observed in animals, in rodent species.

If I could have slide up, please?

The first was in a study of rodents where there was noted to be an increased incidence of liver

tumors -- adenomas, blastomas, adenocarcinomas. This appeared to be a similar effect to that observed with other medications that do induce some CYPs isoenzymes, in particular, CYP2B. It's a phenobarbital-type effect where one sees increased cell proliferation leading to tumors in these animals.

These are not felt to be of clinical relevance, and, in fact, with respect to phenobarbital, where the same types of observations were made pre-clinically, there's not an association in the clinic, in humans, with tumors.

With respect to the clinical experience that supports that with respect to pirfenidone, it's summarized on the bottom of this slide. There have been no cases of primary liver carcinoma seen in any of the immediate studies, and only isolated cases seen in the Shionogi experience.

So at least in our view, this is not felt to be of clear clinical relevance.

DR. CALHOUN: Okay. Final question. Ms. Gottesman?

MS. GOTTESMAN: Thank you.

Your data talked about cardiac disorders as a serious adverse event, but I notice you haven't mentioned it today in your presentation. So my question really is twofold.

Can you elaborate on the Shionogi SP3 post-marketing data, and, obviously, in particular, on any long-term cardiac disorders? And can you share any additional safety findings in your open label studies, 002 and 012 relating to this issue?

DR. PORTER: Thank you. Cardiac events were designated an adverse event of interest, as we did see a small imbalance, particularly in the arrhythmia category in the pooled Phase 3 studies. This was somewhat surprising because there is no preclinical evidence of a signal, and there had not been any previous evidence in prior clinical studies.

When we saw that signal, which was small and not of clear significance, we actually went back and collected the ECGs that were done in the clinical studies. The protocol specified that ECGs were conducted, but they were read at the site since there had been no evidence of a problem before. When we saw

this imbalance, we collected those ECGs and had them centrally read and analyzed, and, basically, that showed no increased concerns around the cardiac signal.

I'm going to ask Dr. Kowey to comment on that in just a second. But I want to answer the second part of your question, which is with respect to the long-term safety studies and the Japanese experience in post-marketing study. There's been no evidence of a cardiac signal in any of those studies.

So with respect to what was seen in the trial, let me just comment on that before Dr. Kowey does.

Could I have slide up, please? Actually, no. That's not the slide I want. Could I have SA-11, please? Thank you. Correct. Could I have slide up, please?

So these are the original observations. These are the pooled observations from the two studies that we noted when we unblinded the studies. And this is the cardiac arrhythmia group. When we looked at other cardiac groups, such as cardiac failures,

ischemic heart disease, there was no imbalance.

What we noted on here was the small imbalances that one can see in atrial fibrillation, palpitations, and tachycardia, of interest, most notable in the low-dose group.

So I'll ask Dr. Kowey to actually comment on the significance of these, as well as the central review.

DR. KOWEY: Yes, there we go. There's a lot of tall people over here.

So the company was faced with the question -- I'm sorry. I'm Peter Kowey. I'm a cardiologist and electrophysiologist at Jefferson in Lankenau Hospital in Philadelphia. Sorry. I have no equity interest in this company, and the only way they pay me is by the hour.

So there was a concern about this because of the imbalance that you see, and so there were several tactics. One was to go back and very carefully review all of the cases in the data set by Joel Morganroth, who conducted that review. There was also a very careful re-review of the thorough QT study and the

preclinical information surrounding that. There was also a careful look at, as you suggested, the surveillance data from the Japanese experience, as well as the U.S. experience.

The composite of all of that, after a great deal of due diligence, is that there really isn't anything that would raise a level of concern. For one thing, the arrhythmias that you see here are all different arrhythmias. There's really no common thread. There's nothing that would relate these arrhythmias to any of the preclinical signals or to a QT issue. And then there's really no obvious dose issue here, as well. There is, in fact, no dose relationship between these effects and the doses that were used.

So for all of those reasons, after a very thorough look at this, we conclude that there is not, that we can see, an arrhythmia liability. The caveat, obviously, is this is a relatively small data set and there is just absolutely no way to completely exclude the possibility of a rare arrhythmic event within the experience of this drug or any other like drug.

So we would reserve the notion that we can be completely sure, but as sure as we could be based on the data set.

DR. CALHOUN: Okay. Thank you.

At this time, we're going to take a 10 -- not 15 -- minute break. By my watch, it's 10:25, and so we'll reconvene in this ballroom at 10:35. For the panel members, please remember that there should be no discussion of the issue at hand with other panel members or with any member of the audience.

(Whereupon, a recess was taken.)

DR. CALHOUN: Good morning, again. At this point we will proceed with the FDA presentation. So the presentation will start with Dr. Karimi-Shah.

DR. KARIMI-SHAH: Thank you, Dr. Calhoun. Good morning. My name is Banu Karimi-Shah, and I'm a pulmonologist and critical care physician with FDA in the Division of Pulmonary and Allergy Products. On behalf of the Division, I'd like to thank Dr. Calhoun and members of the committee for being here today to provide your expertise.

You've already heard in great detail about

the clinical development program from Dr. Bradford and Dr. Porter of InterMune. Over the next hour or so, we would like to highlight several aspects of the pirfenidone clinical development program and provide the agency's perspective.

The FDA presentation will consist of three parts. For the first part of the presentation, I will begin by providing a brief overview of IPF and pirfenidone and an overview of the pirfenidone clinical development program. This will be a brief summary, as you've heard most of this from the sponsor.

This will be followed by the statistical discussion of efficacy presented by Ms. Feng Zhou.

Following the statistical presentation, I will return with some clinical perspective on the efficacy analysis, specifically with respect to the challenges interpreting the clinical significance of the primary endpoint and the limitations of the mortality analysis, which you have already heard presented.

To round out the risk-benefit discussion, I

will then give you a brief overview of the safety of this application, and, finally, end with some concluding remarks.

With that as an outline, I'll begin with a brief introduction. And I'll go through this fairly quickly, as I think you've heard a lot of the details from Dr. du Bois.

IPF is a rare, chronic, progressive, diffuse parenchymal lung disease of unknown etiology affecting approximately 5 million patients worldwide. It's defined by a constellation of histopathologic, radiologic, and clinical findings, as defined by the American Thoracic Society in their consensus statement, which is included in your briefing package.

From a histopathologic standpoint, one sees usual interstitial pneumonia on biopsy. From a radiologic standpoint, HRCT shows peripheral bibasilar reticulonodular abnormalities, with architectural distortion, honeycomb change, and traction bronchiectasis.

From a clinical standpoint, this disease affects males greater than females, and usually

presents between 40 to 50 years of age. The hallmarks are slowly progressive dyspnea and nonproductive cough. Progressive fibrosis of the lung leads ultimately to death within three to five years after diagnosis.

Despite the inevitable mortality that results, and as you have already heard, the progression of the disease is variable among individuals, and recent data suggests that chronic decline is punctuated with episodes of acute accelerated decline.

There are currently no FDA-approved therapies for the treatment of IPF. The rationale for treating IPF has been based on the concept that inflammation leads to injury and fibrosis. To date, most treatment strategies have been based on eliminating or suppressing the inflammatory component.

Current medical therapy for IPF is poorly effective, and even what is considered to be the standard of care has not been conclusively shown to alter underlying fibrosis or disease progression.

With this as background, InterMune has

submitted a new drug application for pirfenidone. The proposed indication, as you have heard, is for the treatment of patients with IPF to reduce decline in lung function.

Pirfenidone is a new molecular entity in a new pharmacological class. It is a small, synthetic, nonpeptide molecule whose exact mechanism of action is uncertain. However, the applicant proposes, based upon in vitro and animal studies, that pirfenidone has both anti-fibrotic and anti-inflammatory properties.

A 267-milligram immediate release capsule is proposed for marketing. The proposed dosing regimen is 2403 milligrams per day, or nine capsules, divided into three doses, to be taken with food. InterMune proposes a two-week dose escalation scheme to prevent known tolerability effects, including nausea, dyspepsia, and dizziness, and the specifics of this dose escalation scheme are seen on this slide.

Two pivotal trials, 004 and 006, were submitted by the applicant to support the efficacy of pirfenidone to reduce the decline in lung function in patients with IPF. Both trials were almost

identically designed as randomized, double-blind, placebo-controlled clinical trials to compare the efficacy of pirfenidone compared with placebo.

In trial 004, patients were randomized into three treatment groups, 2403 milligrams per day, placebo, or pirfenidone 1197 milligrams per day, in a 2:2:1 fashion, respectively. In trial 006, patients were randomized into two treatment groups in a 1:1 fashion, to receive either 2403 milligrams per day of pirfenidone or placebo.

All patients were to remain on study treatment from the time of their randomization until approximately 72 weeks after the last patient had completed study treatment. Therefore, duration of therapy for each patient differed, depending on when the patient was randomized into the study.

You've heard a lot of information from the company presented regarding the Shionogi trials, which form the basis of approval for pirfenidone for the treatment of patients with IPF in Japan, particularly the Phase 3 study, SP3.

In study SP3, pirfenidone was studied in a

different formulation, a tablet, and at a different dose. Although the applicant has provided the agency with an English translation of the Japanese clinical study report, they have not provided any patient-level data, including case report forms, narratives, or statistical data sets, for our review, as these are proprietary to the Japanese company. Without the data to review, the agency cannot rely upon the results of SP3 to evaluate the efficacy of pirfenidone.

InterMune did provide the agency with some safety information from the Japanese studies, as well as from previously conducted trials. When relevant, this safety information will be presented, and some of it you have already heard.

Due to the lack of efficacy data from SP3 provided to the agency for review, the agency's presentation with respect to the efficacy will focus on the results of the Phase 3 trials conducted by InterMune, trials 004 and 006.

Before moving on with a discussion of the Phase 3 trials, it is of note that there were no formal dose-ranging trials in the clinical program.

InterMune stated that the dose of pirfenidone in the Phase 3 trials was derived from the 1800-milligram-per-day dose in the Shionogi study, weight normalized to the expected body weights in trials 004 and 006. The lower dose of study medication, 1197 milligrams per day, was included as the lowest dose which could have been effective and to provide additional safety information.

We understand that dose ranging in IPF patients for the proposed indication can be challenging, given the small number of patients available for participation in clinical trials, and the need for long-term clinical trials to evaluate a treatment effect, as there are no established pharmacodynamic surrogate endpoints.

In the absence of formal dose ranging studies, the applicant's strategy for including a lower dose in trial 004 was an acceptable way to acquire some exploration of dose and additional safety information, albeit in Phase 3.

The enrollment criteria in trials 004 and 006 were summarized by the applicant already. I will

just make note that the clinical, radiographic, and/or pathologic diagnosis of IPF was required, and the FVC and DLCO parameters are as listed here. As a question was brought up earlier on this, the inclusion criteria did include that patients have no evidence of improvement in their FVC over the year preceding study entry.

Concomitant medications used to treat IPF for the most part were prohibited, with the exceptions of certain situations which were defined a priori by the sponsor, including acute respiratory decompensation, acute IPF exacerbation, and progression of disease. And the concomitant medications used during these times is summarized in my briefing document.

Based on the accepted clinical practice guidelines and the ATS consensus statement, we felt that these inclusion criteria with respect to the diagnosis of IPF were acceptable.

In this slide, I have just summarized selected baseline characteristics that have already been presented by InterMune. Again, a total of 779

patients were randomized in the two Phase 3 trials, 435 patients in 004 and 344 patients in 006. FVC and DLCO were similar across treatment groups and across trials.

Here, I've presented the smoking status. And you can see that for the most part, greater than 60 percent or so were previous smokers across treatment groups and across trials, with the next most common group being patients who never smoked, followed by patients who are currently smoking.

In terms of differences between trials, you can see here that supplemental oxygen was used by a larger proportion of patients in trial 006, approximately 28 percent, versus 14 to 17 percent in trial 004.

Another difference which is not shown in the slide, but has been raised today is that there were more patients in trial 006 who were enrolled at U.S. sites, 97 percent in 006 versus 65 percent in 004.

Again, this table summarizes criteria used to make the diagnosis of IPF. And you can see here 88 to 95 percent of all patients in both studies and

across all treatment groups had a definite diagnosis of IPF by HRCT. The proportion of patients who had a surgical lung biopsy ranged from 37 to 55 percent, but among those who had a surgical lung biopsy performed, greater than 90 percent had a definite diagnosis of usual interstitial pneumonia, the pathologic hallmark of IPF.

Based on this baseline data, we are in agreement with the sponsor that the Phase 3 patient population has a confident diagnosis of IPF.

The efficacy endpoints for both trials are summarized here. The primary efficacy parameter was the absolute change in percent predicted forced vital capacity, or FVC, from baseline to week 72. The primary comparison was between pirfenidone 2403 milligrams per day versus placebo. Again, the 1197 milligram-per-day was included for dose exploration and additional safety information.

Many secondary endpoints were pre-specified. Our discussion, from the agency's perspective, will emphasize the secondary endpoint of progression-free survival, as this was the only endpoint to achieve

statistical significance in concert with the primary endpoint in that trial.

Survival was pre-specified by InterMune as an exploratory endpoint, and was examined at several different time points throughout the study period. Although survival was designated as an exploratory endpoint, given the importance of this endpoint in the IPF patient population, mortality was examined in detail to determine whether either study, individually or pooled, showed a significant mortality benefit. Analysis of all-cause mortality was pre-specified, while IPF-related mortality was examined as a post hoc analysis.

I will discuss the primary endpoint and mortality in more detail in just a bit. But now I would like to turn the presentation over to Ms. Feng Zhou, the agency's statistical reviewer.

MR. ZHOU: Hi. My name is Feng Zhou. I'm the statistical reviewer for this application.

Dr. Karimi-Shah has presented background information about this application. The focus of my presentation is the efficacy result of the studies 004

and 006. I will briefly describe the statistical method used by the applicant, discuss some statistical issues identified during review of the application, and I will present the results from both studies.

Study 004 and 006, as you heard from Dr. Karimi-Shah and the applicant, are identical in design, except study 004 included a lower dose, 1197 milligrams per day. The primary endpoint for both studies was the absolute change from baseline to week 72 in percent predicted FVC.

The primary analysis was conducted on all treated patients. The goal is to compare the absolute change in percent predicted FVC from baseline to week 72 between the pirfenidone 2403 milligrams per day and the placebo. And this is done by using rank analysis of covariance, stratified by geographic region, U.S. versus rest of world.

I'm going to present the result for high dose of 2403 milligrams per day compared to placebo.

The protocol pre-specified the approach to handle missing assessment as follows: The data was missing as a result of death, or they ranked worse

than data missing for reasons other than death. And the rankings were based on the time to death, which the shortest time until death had the worst rank.

The missing data for reasons other than death, such as a missing visit, early withdrawal from study, including missing values due to lung transplantations, were imputed with average measurement for similar patients from all treatment groups at the same time point. We considered this approach to be reasonable. In my presentation, I'm going to present results using this approach.

Of note, the applicant also conducted several supportive analyses to the primary endpoint. Also today, applicant presented some post hoc analysis results.

The following are the secondary endpoints applicant examined: time to worsening IPF, progression-free survival, categorical assessment of the absolute change in percent predicted FVC from baseline to week 72, and so on.

In addition, we also evaluated all-cause mortality between the treatment groups. This is one

of the endpoints to assess the benefit of pirfenidone in IPF patients. Log rank tests and the Cox regression stratified by geographic region were used to analyze those time to event analysis endpoints.

In each study, applicant did not apply any multiplicity adjustment for the secondary and exploratory endpoints. Their reasons are stated in the study report: the limited information in the literature about assessing IPF; the lack of the regulatory precedent to guide in the selection of endpoint for IPF.

However, in amending the protocol, they considered an approach to evaluate a secondary endpoint using pooled data in addition to individual study analysis. The applicant stated that if the primary efficacy analysis is absolute change in percent predicted FVC from study 004 and from study 006, each showing efficacy at a p equal to 0.0498, then the secondary outcome variables would be analyzed using pooled data from both studies, in addition to the individual study analysis. Please keep this in mind when I talk about efficacy results.

In study 004, the patient receiving pirfenidone had a smaller mean decline from baseline in percent predicted FVC compared to those receiving placebo at week 72. This represents an absolute difference of 4.4 between the two treatment groups.

In study 006, in contrast, there was no statistically significant difference in the mean decline from baseline in percent predicted FVC in patients receiving pirfenidone compared to those receiving placebo at week 72.

This figure represents the mean change from baseline in percent predicted FVC at each visit. The Y axis shows the mean change from baseline in percent predicted FVC. The X axis shows the corresponding weeks in which FVC measures were collected and reported.

The solid blue line represents the pirfenidone arm, and the solid red line represents the placebo line for study 004. The dashed blue line represents the pirfenidone arm and the dashed red line is the placebo arm for study 006. This color code is used in all my presentation.

In study 004, which is the solid blue and red lines, the change from baseline in percent predicted FVC in the pirfenidone arm appears to separate from placebo arm starting at week 12. In study 006, in contrast, the mean change from baseline in percent predicted FVC in the placebo arm and the pirfenidone arm, which is dashed red and blue lines, appears to come together after week 24.

I also performed a continuous response analysis at week 72. In each study, continuous response curves for each treatment arm are plotted. All patients who dropped out from treatment due to death or lung transplantation were considered non-responders -- that means the highest decline in percent predicted FVC -- and other missing values were imputed using pre-specified imputation methods.

The X axis shows the decline in percent predicted FVC from baseline at week 72, and the Y axis shows the corresponding percentage of patients achieving that level of percent predicted FVC decline or greater.

The positive treatment effect of pirfenidone

was demonstrated by consistent separation of the curves across different levels of the response in study 004. As an example, in the category of having at least a 10 percent decline in percent predicted FVC, there are 20 percent of pirfenidone-treated patients that have at least a 10 percent in percent predicted FVC, compared to 35 percent in placebo. But this evidence is not seen in study 006.

This graphic shows the percentage of patients who had at least a 10 percent decline in percent predicted FVC from baseline at each visit from both studies. In consultation with the clinical team, the cutoff point of 10 percent or more was chosen. Dr. Karimi-Shah will talk about this in detail later.

This responder analysis confirmed the primary analysis result, which is pirfenidone shows some benefit in reducing lung function decline in study 004, but not in study 006.

From a statistical standpoint, since only study 004 showed efficacy in the primary endpoint, in accordance with the protocol specifying a multiplicity plan, analysis of the secondary endpoint using pooled

data should not be considered confirmatory.

In addition, because the primary endpoint in study 006 did not win, no result from secondary endpoint analysis from that study can be considered statistically significant.

Progression-free survival, defined as death or disease progression, which is the first occurrence of any of the following events: at least a 10 percent absolute decline in percent predicted FVC, or at least a 15 percent absolute decline in percent predicted DLCO, or death.

In study 004, treatment with pirfenidone resulted in a higher proportion of progression-free survival than treatment with placebo, which is 74 percent versus 64 percent of patients, respectively. Hazard ratio was 0.64, which represents a 36 percent relative reduction of a combined risk of disease progression or death before disease progression compared to placebo.

However, exploring individual components of this combined endpoint, the reduction appears to be mainly due to disease progression; in particular, a

decline of at least 10 percent in predicted FVC occurring in 16 percent of the patients in the pirfenidone group compared to 23 percent of patients in the placebo group. Also, progression-free survival is one of many secondary endpoints analyzed by the applicant.

Now, I'm going to shift focus and talk about the mortality. Unlike other secondary endpoints, mortality can reach the status of a primary endpoint. The only reason they are not designated as a primary is because we lack the power to detect a clinically important effect on mortality. But if it observed a statistically significant finding on the mortality, it's important.

In both studies, all-cause mortality was pre-specified as an exploratory endpoint. The IPF-related death was analyzed post hoc by the applicant. We evaluated all-cause mortality and IPF-related death from study 004 and study 006 individually, and from pooled data.

Deaths are classified into three groups. On-treatment death, that is defined as death occurring

between the first dose of study treatment and the 28 days after last dose of study treatment, the same definition as treatment-emergent.

Treatment period death is defined as death occurring between the first dose of study treatment and before the latest date of August 20, 2008, the last dose of study treatment.

The vital status at end of study death was defined as death occurring between the first dose of study treatment and before end of study.

There's no big difference in the result between the treatment period death and the vital status at end of study death. Therefore, I'm only presenting the result from on-treatment death and the vital status at end of study.

From each study, there is evidence of a reduction in risk in the pirfenidone group compared to placebo in on-treatment death. The hazard ratio is 0.7 for study 004, and 0.6 for study 006. However, the 95 percent confidence interval of the hazard ratio includes 1, and the value of that corresponds to a more favorable outcome with placebo. So that the

direction of difference in the risk, if any, is not known with much confidence.

At the end of study period, the death rate was higher in the placebo group compared to pirfenidone group in study 004. In study 006, the death rates were similar between the two treatment groups. A similar conclusion was observed when patients with lung transplantation were included in the mortality count.

In next two slides, I'm going to present a Kaplan-Meier survival curve for the all-cause mortality using pooled data during the on-treatment death period and during the entire study period, which is referred to as the vital status end-of-study period.

In this graphic, the Y axis is the probability of being alive, and the X axis is the corresponding treatment weeks. The red line represent placebo, and the blue line represent pirfenidone.

The risk of the on-treatment death is slightly lower in the pirfenidone arm than in the placebo arm. The hazard ratio comparing the two

treatment groups is 0.6. However, the 95 percent confidence interval hazard ratio includes 1, and the values that are corresponding to more favorable outcome with placebo. Therefore, the direction of the difference in risk, if any, is not known with much confidence.

For the vital status end-of-study death, the risk for death is also slightly lower in the pirfenidone arm than in the placebo arm. The hazard ratio comparing the two treatment group is 0.8. However, like on-treatment death, the 95 percent confidence interval of hazard ratio also includes 1. Therefore, the benefit of pirfenidone on all-cause mortality is uncertain.

For the on-treatment IPF-related death, the placebo arm had a higher death rate compared to pirfenidone arm. The hazard ratio was 0.5 for both studies. Again, the 95 percent confidence interval of the hazard ratio includes 1. So that a direction of the difference in the risk, if any, is not known with much confidence. In addition, IPF-related deaths was not adjudicated. Dr. Karimi-Shah will talk about this

in detail later.

For the vital status at end-of-study period, the death rate was higher in the placebo group compared to the pirfenidone group in study 004. In study 006, death rates were similar between the two treatment groups. The Kaplan-Meier survival curve for the IPF-related deaths using pooled data during on-treatment period and then during entire study period are presented in the next two slides.

The risk of on-treatment IPF-related death is lower in the pirfenidone arm than in the placebo arm. Based on the log rank test, the survival curves between the pirfenidone and the placebo differ. The hazard ratio comparing the two treatment groups is 0.5, with a confidence interval lying entirely below null. However, the IPF-related deaths were not adjudicated. It is difficult to make a definitive conclusion about this result.

From vital status at the end-of-study period, the risk of the IPF-related death is slightly lower in the pirfenidone arm than in the placebo arm. The hazard ratio comparing the two treatment groups is

0.7, with a confidence interval that includes 1. Therefore, the benefit of pirfenidone on IPF-related deaths is not known with much confidence.

In summary, from the primary efficacy endpoint in study 004, there is a statistically significant difference in favor of pirfenidone over placebo on the change in lung function. This positive finding was not replicated in study 006.

For the secondary endpoint, in study 004, there is a treatment difference on progression-free survival in favor of pirfenidone. However, this endpoint is one of many secondary endpoints, and the positive finding was not replicated in study 006.

For mortality, all-cause mortality is a pre-specified endpoint. The benefit of pirfenidone on all-cause mortality is uncertain. There is some suggestion of a benefit of pirfenidone from post hoc analysis of on-treatment IPF-related death. However, causes of death were not adjudicated.

Thank you.

DR. KARIMI-SHAH: Thank you, Ms. Zhou. I will now begin the third and final portion of the

agency's presentation. I'll begin with a critical perspective on the applicant's analysis you have just heard presented, and then move on with a brief overview of the safety findings in this application, and then some concluding remarks.

For this portion of my discussion, I will concentrate on providing some clinical perspectives on the primary efficacy analysis and the mortality analysis, so I'll begin with the primary endpoint.

As you've heard, the primary efficacy analysis was the absolute change in percent predicted FVC from baseline to week 72. The results from trial 004 showed a statistically significant back and forth of pirfenidone 2403 milligrams per day over placebo, and trial 006 showed no statistical difference.

In trial 004, the placebo group declined about 12 percent, while pirfenidone 8 percent, the absolute difference being 4.4 percent. Is the difference clinically important? I think that's the question of the day. And what would constitute a clinically meaningful difference? I think it's fair to say that these questions are under active

discussion in the academic and clinical community.

As you've already heard, published literature suggests the significance of a threshold of greater than or equal to a 10 percent decline in forced vital capacity both as a marker for disease progression and as a predictor for mortality. And I have listed some of the references here, and these have also been listed by the sponsor. The ATS International Consensus Statement also uses a 10 percent threshold in vital capacity to define a response to therapy.

I think it's important to remember that these analyses have limitations, and that they have been either retrospective subgroup types of analyses or done with a small number of patients, or produced by expert consensus rather than prospectively validated. But based on what we know to date, this may be a reasonable threshold to define disease progression, and, in fact, it is what we used in our responder analysis, if you'll recall the curves presented to you just now by Ms. Zhou.

Although lung function does appear to be a

logical choice for measurement of IPF clinical outcomes, FVC has not been prospectively validated as an outcome that is clinically meaningful to patients or a surrogate for a clinically meaningful outcome.

The more difficult question is that minimal important differences in lung function parameters in patients with IPF have not been formally established. So the clinical significance of the treatment effect, based on lung function parameters, is open for discussion, and we look forward to your comments on this issue today.

The difficulty in interpreting lung function as a primary endpoint in IPF clinical trials raises the more fundamental issue of endpoint selection in IPF trials.

Given the fatal prognosis of this disease, it's generally agreed upon that mortality is the ideal and most compelling efficacy variable in IPF clinical trials. But we acknowledge the challenges in using mortality as an endpoint.

To date, there are no established or prospectively validated surrogate endpoints for

mortality in IPF. The agency has, therefore, taken the stance that clinical development programs for IPF should emphasize those outcomes which are clinically meaningful to patients such as death, lung transplantation, hospitalizations, et cetera. Additionally, the agency has encouraged investigators to measure mortality in their clinical trials as a means of validating the endpoints they have chosen.

I'd like to take this opportunity to say a few words about the choice of primary endpoint. The division has had multiple interactions with the company throughout the course of the development program, at which times we cautioned the company regarding the limitations of using FVC decline as a primary endpoint.

Most recently, prior to submission, at what we call a pre-NDA meeting, we reiterated that a decline is FVC is not an established surrogate for mortality, and that the clinically meaningful difference in FVC is not known.

The division stated at that time, since the applicant had chosen to use FVC as a primary endpoint,

the totality of the data would be examined to determine what was driving the primary endpoint. It would also be important for the secondary endpoints to support the primary endpoint. In addition, for a drug that is modifying a disease, it would be important to evaluate the pattern of FVC decline. These limitations of using FVC as an endpoint should be kept in mind when interpreting the results of the primary endpoint.

With that as background, I'd now like to shift focus onto the analysis of mortality. As Ms. Zhou and I have stated earlier, mortality was pre-specified as an exploratory endpoint. All-cause mortality was examined on treatment and at vital status end-of-study assessment. I'll go into a little bit of a discussion about the distinctions between the two different time periods in just a moment.

I'd like to say that although this is designated as an exploratory endpoint, given the clinical importance of this endpoint, mortality was examined in some detail, as you have seen, to determine whether either study individually or the two

studies pooled together showed a significant mortality benefit.

Demonstrating an effect on survival is, of course, relevant from a clinical standpoint, but from a regulatory standpoint, as well, as this goes to the matter of whether substantial evidence of efficacy has been provided.

I'd like to take a minute now to just discuss the concept of substantial evidence before delving into the mortality analysis in some detail.

The agency's guidance for industry, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," describes what constitutes substantial evidence. This guidance document has been included in your briefing package.

The agency typically requires two studies to provide independent substantiation and replication of results. However, there are situations in which one study may be adequate; for example, a multi-center study of excellent design with highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival.

As you have heard, only one study, trial 004, met its primary endpoint on a change in a lung function parameter. With the definition of substantial evidence in mind, the agency, therefore, examined mortality in detail, despite its designation as an exploratory endpoint, because demonstration of a mortality benefit would be a situation in which substantial evidence of efficacy leading to drug approval could be provided by a single trial.

This slide provides a summary of the mortality analysis as discussed in detail by Ms. Zhou. All-cause and IPF-related mortality were examined, as we've detailed, on treatment and at a vital status end-of-study assessment, again, on-treatment being between the first dose of study drug and 28 days after the last dose of study drug, and vital status end-of-study being at the very end of the study.

As you can see, neither trial individually showed a clear survival benefit for pirfenidone-treated patients, whether examined on-treatment or at the vital status end-of-study assessment, as can be seen by the wide confidence intervals, which include

the null value.

When mortality was examined in the pooled population, the rightmost column, there was, again, an unclear mortality benefit with regard to all-cause mortality, but a statistically significant reduction in on-treatment IPF-related deaths.

This finding needs to be interpreted with some caution for reasons that I will go into. But first, I'd like to spend a few minutes discussing the different ways mortality was evaluated in this program, both in terms of timing and cause of death.

In terms of the timing of the mortality assessment, on-treatment versus vital status at the end of study, there are reasons to look at both assessments. If you are looking at death as an adverse event of the drug, then on-treatment may be of interest. However, one could argue that if a drug were having a disease-modifying effect that improved mortality, the effect on survival should persist when measured at the end of study and not just on treatment.

In terms of all-cause mortality versus IPF-

related treatment, all-cause mortality was a pre-specified analysis and is a clinically meaningful endpoint. As such, all-cause mortality has been pre-specified as an endpoint of interest in the few large placebo-controlled clinical trials in IPF patients.

IPF-related mortality has not been defined or consistently evaluated in other IPF clinical trials. In one article that I referenced earlier and has also been referenced by the sponsor, by Collard and colleagues, published in the American Journal of Respiratory and Critical Care Medicine in 2003, included analysis which censored patients dying from causes of death other than IPF. The authors noted in their discussion that an argument can be made that the more clinically meaningful endpoint is all-cause death and not death due to IPF.

The post hoc assessment of IPF-related mortality has many limitations. I will now spend some time discussing this analysis, not because we feel that it is the most clinically meaningful of all the analyses, but because the sponsors provided some evidence that this analysis is supportive of the

efficacy of pirfenidone. And from the agency's perspective, this analysis has several limitations that merit discussion.

First, it is important to note that the death was not adjudicated in the pirfenidone pivotal clinical trials. Investigators at individual sites were asked to indicate via check box on the mortality case report form as to whether a death was considered related to IPF.

As both the applicant and agency's analysis rely on the investigator's assessment as to cause of death, I would now like to discuss this assessment as it applied to the on-treatment IPF-related mortality analysis.

So the cause of death by preferred term for all deaths that occurred on-treatment -- again, that is between the first dose of study drug and 28 days post-study drug discontinuation -- is listed in the table seen here, divided by treatment group for the pooled 004 and 006 population.

As shown here, there were a total of 19 on-treatment deaths in the pirfenidone 2403 milligram-

per-day group, and 29 deaths in the placebo group. The causes of death are listed here: ARDS, arteriosclerosis, bladder cancer, cor pulmonale, hypoxia, IPF, myocardial infarction, pneumonia, pulmonary hemorrhage, respiratory failure, septic shock, and small cell lung cancer-metastatic.

In this slide, I've highlighted those deaths which were assessed by individual investigators as being IPF-related. As you can see, of the 19 deaths in the pirfenidone group, 12 were assessed as being related to IPF. The causes of death assigned were: hypoxia in one case, IPF in six cases, and respiratory failure arrest in five cases in the pirfenidone group.

In the placebo group, there were a total of 29 on-treatment deaths, with 25 being assessed as related to IPF. Causes of death, again, by preferred term, in this group included ARDS in one case, hypoxia in one case, idiopathic pulmonary fibrosis in 14 cases, myocardial infarction in one case, and pneumonia in two cases, and, finally, respiratory failure arrest in six cases.

Because the causes of death in relatedness

to IPF were assessed by individual investigators and not adjudicated, I'd like to draw your attention to the following inconsistencies with respect to pneumonia, pulmonary hemorrhage, and septic shock.

With respect to pneumonia, you'll notice that two cases were deemed IPF-related in the placebo group and unrelated to IPF in the pirfenidone group.

The case that was designated as septic shock, again, was a septic shock that was due to pneumonia on review of the case narrative. This septic shock due to pneumonia was also deemed unrelated to IPF in the pirfenidone group.

I reviewed all of these narratives, these five narratives, in detail for -- or the four -- the pneumonia narratives, the four narratives, and the septic shock narrative in the pirfenidone group, and I didn't note any particular difference in those cases that were IPF-related in the placebo group versus those that were designated as unrelated to IPF in the pirfenidone group.

Just a quick word about the pulmonary hemorrhage case. This was a very complicated patient

with a complicated hospital course, and many of these narratives make an assessment as to whether the outcome was related to study drug or not.

And in that assessment, in the narrative, pulmonary hemorrhage is not assessed to be due to study drug, and the narrative goes into some detail as to why pulmonary hemorrhage is an outcome that can be experienced by IPF patients for various physiologic reasons. So it's unclear why this case would be coded as being unrelated to IPF.

I'd like to just say by way of clarification that the agency has also not blindly adjudicated these cases. I'm not singling out these cases to definitively report a misclassification. Of course, the investigators at the individual sites were making these assessments. I'm only showing these cases to point out an inconsistency due to the fact that these cases of death were not centrally adjudicated.

I'll now move on to the safety portion of my presentation, which will be a quick summary of what you've already heard from Dr. Porter.

This slide provides an overview of the

safety information that I'll present. I'll go into the safety database, patient exposure, deaths from a safety perspective quickly, as I've outlined them already in the efficacy analysis; adverse events, with some mention of hepatic laboratory abnormalities and photosensitivity reactions; and then, finally, moving on to safety conclusions.

The safety database that I will be concentrating on is a randomized subset which consisted of 432 patients treated with pirfenidone, 345 in the high-dose group, 87 in the low-dose group, and 347 placebo-treated patients. Safety information from other studies, whether foreign or from other sponsors, was reviewed and will be mentioned when relevant.

Pooling of data across trials 004 and 006 to examine the emergence of any safety signals was acceptable, because, as you have heard, these trials were relatively identically designed and the patient population was comparable in terms of demographics, baseline characteristics, and dose of pirfenidone.

In the randomized patient subset in trials

004 and 006, the majority of patients in all treatment groups remained on treatment for the planned treatment period. Duration of study treatment was similar between patients treated with pirfenidone 2403 milligrams per day and patients treated with placebo.

The duration of the treatment of patients treated with pirfenidone 1197 milligrams per day was similar to the other treatment groups. That's not shown on this slide.

This table shows the disposition of patients in trials 004 and 006. In both trials, approximately 80 percent of patients completed treatment with pirfenidone and placebo. The most common reasons for discontinuation were AEs and death. More patients in the pirfenidone group withdrew due to adverse events than in the placebo group. The most common AEs that led to discontinuation were IPF, rash, and nausea.

In the lower-dose group, which is not shown here, the completion and discontinuation rates were similar to what was observed for the pirfenidone 2403 milligrams per day, and the discontinuation rate secondary to AEs and death was also similar.

To provide an overview for risk-benefit assessment purposes, I will emphasize death, adverse events, and clinical laboratory testing in the rest of this presentation. Other safety assessments are outlined in detail in my review in the agency's briefing package.

We already talked about the mortality analysis in some detail as it pertained to the efficacy of pirfenidone. Just for safety purposes, on-treatment deaths here are emphasized. You can see that 9 percent of patients died in the low-dose pirfenidone group, 6 percent of patients in the high-dose pirfenidone group, and 8 percent in placebo.

The most common cause of death was coded as IPF. Again, this is a separate issue as compared to whether deaths were IPF-related or not. This is a strict preferred term coding that leads to this conclusion of the most common cause of death. Again, three of eight deaths in pirfenidone group, six in the pirfenidone low-dose group, six of 19 deaths in the pirfenidone high-dose group, and 14 out of 29 deaths in the placebo group.

This table shows an overview of the serious adverse events in the two Phase 3 trials. Approximately one-third of patients experienced a serious adverse event, which is not surprising given the long duration of the trials and the older population with a severe disease and co-morbidities.

Overall, as you can see, serious adverse events were balanced between treatment groups. They were reported more frequently in the pirfenidone group compared to placebo, and the ones that were more common are included here, and you've seen this list: coronary artery disease, chest pain, pneumothorax, et cetera.

A review of the 1997 milligram-per-day pirfenidone group does not suggest a dose response for these particular SAEs. And given the small numbers, no particular safety signal is suggested from these SAEs.

The most common adverse events in the Phase 3 trials that occurred at a higher rate in the pirfenidone 2403-milligram group over placebo are listed here. I'll just point out a quick error on

this slide. This dyspnea should say 20 here and not 10.

As you can see from this list, most of these were GI-related -- nausea, diarrhea, dyspepsia, vomiting -- or constitutional type of adverse events, including fatigue; or dermatologic in nature, rash and photosensitivity. These are the events that also most commonly led to dose modification, and present tolerability issues for patients.

These adverse events are known effects of pirfenidone based on previous human experience with the drug, and the company has outlined specific dose modification and titration criteria that could be employed if and when any of the AEs are experienced.

Photosensitivity was also identified as an adverse event of interest. In photo safety tests, as you have heard, phototoxicity and irritation were noted in preclinical models after the administration of pirfenidone and exposure to UVA light. The severity was decreased by sunscreen application.

As shown in the previous slide, rash and photosensitivity reaction adverse events were more

common in the placebo group -- were more common in the pirfenidone group, excuse me, 2403 milligrams per day, compared to placebo. The majority of the adverse events were mild to moderate in severity. There was one patient with a rash serious adverse event, and one patient with a photosensitivity serious adverse event in the pirfenidone 2403 milligram-per-day group.

The majority of the patients had a single event, and the median duration of being affected was three months. Greater than 50 percent of the affected patients developed the adverse event by week 18 of taking of the drug. And as you have heard, there were no cases of Stevens-Johnson syndrome or toxic epidermal necrolysis.

Liver-related abnormalities were another adverse event of interest identified based on previous human experience with pirfenidone. Fourteen, or 4.1 percent, of patients treated with pirfenidone 2403 milligrams per day developed AST or ALT levels that were greater than three times the upper limit of normal, compared with two, or .6 percent, of placebo-treated patients, and zero patients treated with

pirfenidone 1197 milligrams per day.

Three patients in the pirfenidone 2403-milligram-per-day group and two patients in the placebo group developed transaminase elevations that were greater than five times the upper limit of normal. One patient each in the pirfenidone 2403 milligram-per-day and placebo groups, respectively, had an AST or ALT level that was greater than or equal to ten times the upper limit of normal.

It is also noteworthy that liver findings tended to occur within the first six to seven months of exposure. Of the 14 patients in the pirfenidone group who developed AST or ALT levels that were greater than three times the upper limit of normal, 10 developed the elevations within the first 30 weeks of exposure.

There were no liver deaths in the InterMune Phase 3 trials. However, there was one case in the Japanese development program, as you've heard, that may have been suggestive of drug-induced liver injury, a so-called Hy's law case.

I've just outlined the narrative here. This

was a Japanese study patient who initially received placebo in the Phase 2 trial in Japan, and then was continued on into the open label extension portion to receive 1800 milligrams per day of pirfenidone.

He had no past medical history of liver disease, and liver function tests were within normal limits at the time of study entry into the blinded phase of the trial, and on the first day of pirfenidone 1800 milligrams per day therapy in the open label phase of the study.

On day 49, he developed general malaise and anorexia and became jaundiced. On day 56, the laboratory test results showed marked elevations of AST, ALT, as well as hyperbilirubinemia. There was also moderate prolongation of prothrombin and activated partial thromboplastin times.

On day 56, as a result, pirfenidone was discontinued, and a workup was initiated for other causes of liver injury. An abdominal ultrasound was negative for biliary obstruction, and workup was negative for hepatitis infection.

By day 72, as you've seen in the sponsor's

presentation, LFT abnormalities were improving. However, the patient developed fever with concomitant pneumonia that led to respiratory decompensation and death on day 88.

Pathological autopsy results showed the cause of death to be respiratory failure and pulmonary fibrosis. However, the liver was not sampled on autopsy, so we don't have any report of liver damage in this patient from a pathological standpoint.

I'll now make a few concluding remarks with regard to the risk-benefit of pirfenidone by summarizing the safety and efficacy findings.

The safety profile that was observed in this clinical program occurred in the setting of dose modification guidelines and a management plan for expected toxicities. In this setting, GI and dermatologic adverse events were most common, including photosensitivity reactions, which were mild to moderate in severity.

Abnormalities were also noted in liver enzymes, which generally resolved without sequelae. There was the one case in the Japanese clinical

development program that met the criteria for drug-induced liver injury. Based upon the findings in that patient and what is known historically about pirfenidone, hepatocellular injury due to pirfenidone cannot be ruled out.

This is a summary of the safety findings, which need to be factored together with the potential efficacy of pirfenidone, which is as follows.

The pirfenidone clinical program consisted of two nearly identical clinical trials, 004 and 006, in which the absolute change in FVC from baseline to week 72 was the primary endpoint evaluated. One trial won on the primary endpoint, and one did not.

The treatment effect size was 4.4, which is of uncertain clinical significance. In fact, the choice of endpoint itself raises many questions regarding the interpretation of the treatment effect.

In terms of all-cause mortality, this was a prespecified, clinically meaningful endpoint. Pirfenidone did not show a clear benefit in all-cause mortality either individually or in the pooled trial population.

The pooled results did suggest a benefit on IPF-related mortality only while on treatment, but this was as a post hoc analysis, with no pre-specified definition, where cause of death was not adjudicated, leading to inconsistencies in assessment of IPF-related deaths. Further, the robustness of the data is questionable as this effect did not persist when examined at the end of study in the vital status analysis.

I'd like to close by saying that the agency recognizes the difficulties and challenges in designing and conducting clinical programs for rare diseases like IPF, and we are sensitive to the fatal prognosis and the horrid nature of this disease. We remain committed to promoting the development of safe and effective therapies for such orphan diseases.

Whether pirfenidone is an effective treatment for IPF to reduce the decline in lung function is not entirely clear from the data that has been submitted. Therefore, we ask the committee to consider the following questions.

I'll just draw the committee's attention

that some of these questions are slightly different than what was in your briefing package, and I'll draw some attention to those differences as I go through the questions.

So Question 1: Discuss the efficacy data for pirfenidone.

(a) Include a discussion of what constitutes a clinically meaningful effect size for the change in percent predicted FVC.

And then (b) is a change from what was in your briefing package: Include a discussion of the mortality data.

Question 2 asks you to discuss the safety data for pirfenidone.

Question 3, which is a voting question, asks: Do the data provide substantial evidence that pirfenidone provides a clinically meaningful, beneficial effect in the treatment of patients with idiopathic pulmonary fibrosis to reduce the decline in lung function? If not, what further efficacy data should be obtained?

Question 4, which is also a voting question,

asks: Has the safety of pirfenidone been adequately assessed for the treatment of patients with IPF? If not, what further safety data should be obtained?

Then Question 5 is also a change, which asks: Does the committee recommend approval of pirfenidone for the treatment of patients with IPF to reduce the decline in lung function? If not, what further data should be obtained?

I thank you for your attention.

DR. CALHOUN: Okay. Thank you.

A couple of points of order. Firstly, we're not going to discuss those five questions at this point. We have time for clarification on the FDA presentation at this point.

The second point of order is that we've got three questions hanging from the sponsor's presentation, and I want to get to those. So for those three questions, which are Drs. Mauger, Carvalho, and Foggs, I'd invite you to discuss your question of clarification for the sponsor briefly, and then any questions that you might have for the FDA you can certainly roll in there.

For the rest of the panel, after those three have been dealt with, I really would ask you to focus your questions on clarification for the FDA presentation at this point. We're going to have abundant time in the afternoon to discuss these things in greater detail.

So, Dr. Mauger?

DR. MAUGER: This question is for Dr. Bradford, probably. One of the things you commented on when asked about whether there were predictors of progression was the duration or the recent history of diagnosis. And you showed a significant statistical interaction between recency of diagnosis and treatment effect.

I thought I heard you say that the proportion of patients with a recent diagnosis was the same for the two trials. But in the data in the briefing document, it looks like it's actually quite different. By my calculation, it was 60 percent in the 006 trial and only 47 percent in 004 trial.

If that's correct, is that a large enough difference that you feel it could potentially account

for the lack of responsiveness in the 006 trial?

DR. PORTER: Thank you. And I will ask Dr. Bradford to address that. That's an important question.

DR. BRADFORD: Thank you. You're exactly right. Thank you, Dr. Porter. You're exactly right. Slide up, please. There was an imbalance across the two studies with respect to time since IPF diagnosis.

This is a summary here comparing the 004 and 006 baseline characteristics with respect to those that had some level of difference between the two studies. And you can see the first line there, diagnosis of IPF within one year of study entry. There were more patients in the 006 study that had been diagnosed within one year.

Looking at the subgroup analyses, there was a statistically significant interaction between this covariate, dichotomized where you see it, and pirfenidone treatment such that patients diagnosed within one year had less treatment effect than patients diagnosed more than one year prior to study entry.

So the directionality of the imbalance, coupled with the directionality of the treatment interaction, would predict less of a treatment group difference in 006, consistent with what was observed.

I will say, in the context of everything else we've done, we think this is a potentially contributing factor. However, we're not convinced that this is the sole factor that drives the differences observed at week 72.

DR. MAUGER: As a follow-up, was there a correlation between time since diagnosis and baseline FVC?

DR. BRADFORD: That's a good question. I'm not sure we have data to address it. If I could put that on the list for after lunch, as well.

DR. CALHOUN: Dr. Carvalho?

DR. CARVALHO: Thank you. I have three questions, and they all pertain with additional outcomes information.

The first question is: Do we have any other information on outcomes in the open label, as well as the post-marketing studies, in either the Japanese,

which was for 52 weeks, I believe, and the multinational studies, which were about 108 weeks?

The second question is: In the patients that have to have a dose reduction due to side effects, adverse effects, were those patients analyzed separately to see what their outcomes were?

The third question pertains to smoking. And one of the panelists already asked about smoking, and I see that the numbers of patients were evenly matched across the board.

But I wonder if there's a subset that was analyzed for outcomes and adverse effects, just in smokers.

DR. PORTER: So if I could just clarify. On your first question, you asked about other outcomes in the open label studies. Just to clarify, are you talking about other efficacy outcomes in addition to what we've discussed?

DR. CARVALHO: Mortality, 6-minute walk, and FVC.

DR. PORTER: Okay. And then on the second question, you asked about dose reductions and whether

they were analyzed with respect to, and I missed the second part. Efficacy, safety?

DR. CARVALHO: Same parameters.

DR. PORTER: Okay. Same parameters. And the third question on smoking.

With respect to other outcomes in the other studies, with respect to the open label studies, we don't have a comparator group. And so given the heterogeneity of this disease, it's difficult to draw conclusions around outcomes. We do do safety assessments and assess lung function, but with no comparator, it's difficult. So I can't really comment on additional outcomes from those studies.

With respect to your second comment, we have looked at the dose modifications both with respect to safety and efficacy. I showed some of that data with respect to safety this morning. In general, dose modifications were quite effective in adverse events, resolving it. And overall, we saw general comparable rates to resolution of adverse events in the face of dose reduction between the two treatment groups.

DR. CARVALHO: Did those patients that had

dose reductions, did they have the same outcomes as the rest of the patients that did not?

DR. PORTER: I'll ask Dr. Bradford to address that question with respect to outcomes.

DR. CARVALHO: Thanks.

DR. PORTER: Then I'll also ask Dr. Bradford to address your last question with respect to smoking.

DR. BRADFORD: With respect to the relationship between dose modifications and efficacy, we have looked at that. I'll share some data with you. I will point out that, really, the best and most robust estimates we do have on that are from the intent-to-treat analyses, which you've already shown. Slide up, please.

Here's an analysis looking at relationships between mean daily dose and change in FVC. I'll point out the last row on the slide there, difference in mean change based on three different strata of mean daily dose. What one sees there is that there's a treatment effect in favor of pirfenidone over placebo in all three of these strata.

I will point out, as is shown under the

placebo group, that there is a relationship independent of active treatment between mean daily dose and change in FVC, as you see on the first row there.

With respect to your second question, around smoking, we have looked at this issue. There's no interaction between treatment and smoking, either current, where there's not very many patients, or a past history of smoking.

DR. CALHOUN: Dr. Foggs?

DR. FOGGS: Relative to the smoking, since that was the last question that was posed, even though there's no correlation and association with current smoking or past smoking, notwithstanding the fact that two-thirds of the participants in the study who received the drug were smokers in the past, and notwithstanding the fact that heterogeneity of the disease in and of itself, in the absence of a biomarker for longitudinal assessment, makes it difficult to interpret some of these outcomes, do you have any correlation with regards to the total number of pack years that the individuals who did smoke who

participated in the study, past and present, had any therapeutic correlation relative to the response of the FVC to pirfenidone?

In other words, if you take the total number of pack years that the person smoked, does that have any bearing, using retrospective analysis, on the response of the patients to pirfenidone as it relates to any of the data concerning the delta FVC?

DR. PORTER: I appreciate the question. We don't have that data to do that type of analysis.

DR. CALHOUN: Okay. Now, we're going to move to questions strictly related to the FDA presentation and clarifications thereof.

Dr. Hendeles?

DR. HENDELES: Thank you. You mentioned that there were patients discontinued because of IPF. Could you explain what that means and what the impact of that is on the data analysis, please?

DR. KARIMI-SHAH: I'm sorry. I just want to clarify. You want to know what the definition of that --

DR. HENDELES: I didn't understand what you

meant by people withdrawing from the study because of IPF. I thought I heard you say that. Maybe I misunderstood.

DR. KARIMI-SHAH: No, no. I did say that. I was just trying to clarify what you wanted for an answer.

When patients discontinued from the study, a reason for discontinuation was asked and the reason is usually coded by a preferred term in a coding dictionary. And in this program, the preferred term that led to discontinuation for those patients was actually idiopathic pulmonary fibrosis.

The exact definition of that term, I'm sorry, I don't know. But that's what I was referring to when I talked to the discontinuations for that reason.

DR. HENDELES: So what was the impact of that on the data? Presumably, they were failing -- the drug was failing to have a protective effect, or the patients got worse while they were taking the drug. What was the impact on the analysis, or was the number too small to make a difference?

DR. KARIMI-SHAH: I think the number of patients that discontinued were small in that regard, and I don't think that that affected the data analysis.

DR. CALHOUN: Dr. Honsinger?

DR. HONSINGER: Three questions. One, you didn't discuss the quality of life data at all that was submitted in the data that we had. As I look at this disease, we ask, when we're treating these patients, are we really prolonging their life or are we postponing their death? And I think quality of life data is very important here. And from the data we had, it didn't look like it was very important.

And the second question is: We're talking about a drug that has significant adverse effects, and we need to know which patients it's going to help, if there's any way we can identify those patients that are going to benefit.

Looking at the data you showed us, it looked like the patients who were younger might have had greater benefit than the patients who were older, and I wonder if that's a different population.

In my limited experience with this disease, I've seen several families that have a genetic propensity to the disease that seem to be different than those who seem to have it de novo. And they often happen at a younger age. I wonder if there was any evidence in the data looking at familial incidence in that younger group.

The third question: Is there a way we can look at patients and their lung function data? We're presented lung function data at 24 weeks. Would there be benefit in looking at lung function data at three months instead of the 24 weeks and saying, these are the patients who are going to benefit? Can we look at that early data to see if there are patients that benefit later on or if they don't benefit in the first -- if they continue to deteriorate in that first three months, should they be dropped from the drug?

DR. KARIMI-SHAH: I'll try to address a couple of these questions. And then for the second question, I might turn it over to the sponsor.

So your first question was in regard to quality of life data. And in this disease, I'll agree

with you that quality of life is important, and the distinction of averting death or prolonging life is a real one.

The reason we didn't go into it from a regulatory standpoint is we don't have any hard endpoints to look at for quality of life and what a meaningful difference between a treatment that has an effect and a placebo group would be in quality of life parameters for IPF.

There are certainly questionnaires and quality of life measures that are out there. But we don't know what the minimally important clinical differences in those measurements would be in patients with IPF.

So while I'll agree with you, on a global scale, quality of life is very important in many disease processes, including this one, we just don't have any data by which to judge a treatment difference.

Then with regard to your third question about looking at the benefit of earlier data to predict what happens later, perhaps at three months, I

think a lot of these types of analyses have been done retrospectively on a number of studies, and hypotheses have been generated as to what happens and whether these changes are predictive of mortality.

But again, we don't know this in a prospective fashion. And so it would be valuable to look in a prospective fashion and see if these correlate with mortality later on, or other clinically meaningful outcomes later on.

Then in terms of a subgroup analysis versus whether younger patients or older patients did better, we didn't perform that. But I'll turn it over to the sponsor to see -- I'm sure that they have some data regarding the breakdown in age groups.

DR. PORTER: I think with respect to the issue of age, in the subgroup analysis that Dr. Bradford showed, both age groups did benefit. And I think that's the important point.

I think the question, the larger question, that you're asking is around what patients benefit most, how do we choose which patients and how do we treat patients with this drug, because you alluded to

a three-month period and that type of approach, perhaps.

I think it would perhaps be best for me to ask Dr. du Bois to comment on this in terms of how he sees the data relative to your questions.

DR. DU BOIS: Thank you. I think the question is how do we go about treating patients. And I think the concept of trying to identify a group who will benefit most is obviously a very attractive one. And there are some data that would suggest that those individuals who deteriorate, as we've talked about, by 10 percent or more, those individuals do appear to have the risk of having a worse outcome in one year.

But in practice, it becomes much more tricky, because once patients have lost lung function, it doesn't come back. And so the way in which we tend to do it in clinical practice is if a patient presents to us with no previous data, then we look at the severity of lung function and decide, with the patient, whether the pros and cons of any therapy that we would wish to recommend would be more beneficial than not.

Occasionally, we do have the opportunity to see patients where there is some propter hoc lung function data, and then that gives us the advantage of intervening and seeing if that stabilizes decline.

So while I believe that the theory of trying to identify a group who might get worse more quickly, and, therefore, benefit is very attractive, in practice it's very much more complicated. And at any one point in time when you see a patient, you cannot at the moment -- there are no biomarkers, there are no solid markers that would predict subsequent outcome.

So as I say, the practice we use is to assess those with mild to moderate disease, recommend therapy. If we do have a glide path -- and we plot them all out -- if we do have a glide path, that gives us added information about when one commences therapy. But it does remain a really rather imprecise art.

If I could just have the slide up that just makes the point of the heterogeneity of behavior patterns? If you could just advance this and show the first -- here's an individual who -- this is in a previous study of Interferon gamma.

Here's an individual who, over the course of a 72-week study, just didn't deteriorate at all. Another individual, please. Somebody who started at a very similar baseline level slowly deteriorated and then accelerated. And then just the last one, to make the point. And here's an individual who deteriorated, became stable, and deteriorated again.

If you look at the enormity of this spaghetti plot, it just emphasizes the massive heterogeneity. And we don't have a predictor.

DR. CALHOUN: Okay. I have two questions for the agency. The first is that you talked about the lack of adjudication of IPF-related deaths as an interpretive problem. And my question around that is: Do you believe that the investigators were unblinded because of a differential adverse effect rate or some other reason, and that, therefore, there was bias in the adjudication of the IPF relatedness or not?

Because if not, I guess I would figure that imprecision in the determination of IPF relatedness would tend to regress toward the mean and minimize differences, as opposed to artifactually produced

differences.

The second question turns on mechanism of action. And the sponsor didn't talk about this this morning, and I wondered if the agency might have dug into the putative mechanism of action and potential adverse events related thereto.

Firstly, it was indicated that this was a TGF-beta inhibitor, and, therefore, one might wonder whether there was some signal around normal wound healing. And there may be no tools and no metrics to look at that, but it would be interesting for the agency to dig into that a little bit, number one.

The second and perhaps more clinically relevant piece is that it was also listed as an TNF-alpha inhibitor. And we know from the experience with our presumably more potent TNF-alpha inhibitors that there is sometimes an infection signal. So has the agency looked into that?

DR. KARIMI-SHAH: I'll just address your mechanism of action question first. We did not dig into that any further than the information that the sponsor has provided. I will say that, as Dr. Porter

pointed out, in terms of infection, this is presented in my portion of the briefing package. But it was fairly well-balanced among all treatment groups. There was no particular dose response that we saw from low dose to high dose of pirfenidone.

About 60 percent or so of patients had infections across all treatment groups. And I think the most common ones, if I recall my briefing document correctly, were -- sinusitis was one of them. But, again, well-balanced across all treatment groups and trials.

So I don't have any more information for you about the wound healing, which would be affected if this was a TGF-beta inhibitor. All I can say is that in the information that was provided to us by InterMune, the point was made that the exact mechanism of action of this drug is really not known, and what they do know is based on in vitro and animal data. So I think that exact mechanism of action is sort of not strictly defined at this point.

Then moving on to your first question about the adjudication, I think rather than pointing at a

particular bias, I brought up those cases only to show that because the cases were not centrally adjudicated, that there were inconsistencies. And I think it's hard to read the narratives and understand why one pneumonia would be related to IPF and another pneumonia would be deemed unrelated to IPF.

In my mind, a disease which destroys lung architecture makes you prone to pneumonia. And so in that case, they should be all related to IPF. But that's just my personal opinion.

So I raise those as inconsistencies. And I agree with you that if they were just at the individual sites, that that should regress towards the mean. But there were such small numbers, so inconsistencies in a small number of cases create somewhat of an imbalance.

So I'll end with that. I hope that answers your question.

DR. CALHOUN: Dr. Chowdhury?

DR. CHOWDHURY: If I can just add a few more comments to the response that has been made.

I think as far as the death goes, if you

look across the study centers and study sites, there were not too many deaths in a center or a site. So for a particular physician to be biased in one way or the other is very difficult to make that point. And the adverse effects where they don't blind the patient or physicians, it's very difficult to make.

The point that we are raising is exactly what Dr. Zhou mentioned, is across centers, seemingly similar kind of death potentially could have been checked off in either way. So that is the point.

To comment on your mechanism of action question, we have not systemically gone into all the available literature to find the potential mechanism of action for the drug. Perhaps the company may comment on that. But just to let you know that this particular molecule, although it is a new molecular entity that we are bringing up here for a specific indication, has actually been around for a very long time and has been investigated for decades for varieties of conditions.

So it is not a new molecule in that sense, and pretty much it is known. But I am not aware from

the literature, which one can reference, we know exactly how the drug works. Thank you.

DR. CALHOUN: Dr. Platts-Mills?

DR. PLATTS-MILLS: Thank you. I've got three questions.

Is there any evidence in the data for a rebound effect when the drug is stopped? That is, is there any suggestion that exacerbations occur at that time when the drug is stopped, or that patients who appear to be doing well on the drug do well and continue to do well?

The second issue: You argued that the real reason is not for accepting FVC, and yet FVC correlates very close -- well, correlates well with increased walking distance, and clearly increased walking distance is a good outcome, certainly in this disease, and may well be related to overall health.

I agree with your arguments against using the specific data, and I would point out that actually in 006, slide CE-21 shows 11 deaths from IPF in 006 compared to one in the pirfenidone group, which would be highly significant. So obviously, your argument

for using overall mortality is very striking. Nonetheless, mortality data consistently favors the drug.

DR. KARIMI-SHAH: For the first question that you asked regarding whether there's rebound effect when the drug is discontinued or whether patients experienced exacerbations, I don't have that data, and perhaps the company can speak better to that.

I can address a little bit, I think, of your second point. I want to emphasize that I'm not coming down on the side of FVC as not being a good outcome. I'm trying to say that we don't know if it's a good outcome. It may be. And I agree that it does correlate with things such as the walking distance, as the company has shown.

But again, I don't know what a clinically importance difference in the 6-minute walk distance is. And so, again, we have to correlate with things that we can identify as being clinically meaningful, and a lot of these correlations, again, are done in small numbers of patients in retrospective ways. So

these analyses are limited for those reasons.

I think it's very logical to look at FVC as an outcome, because it makes sense, lung function in a disease where you're losing lung function and you're losing lung tissue. But we just don't know what the clinically meaningful differences are, and that's the point that I was trying to make in my presentation.

Then finally, I just wanted to clarify. What exactly are you asking of me with your third question in terms of the mortality? If you could just clarify that for me again.

DR. PLATTS-MILLS: I had the impression that you were suggesting there was no mortality difference. But the data seems to be consistently in favor of the drug in mortality, that there's no suggestion of an effect the other way. So that although maybe you don't have overall significance, it's extremely difficult to get significance in mortality data.

DR. KARIMI-SHAH: I think that's right. I think the point that Ms. Zhou and I were making is that although numerically, the numbers for all-cause mortality do go in the right direction, the confidence

intervals are wide. And so because of that, we can't statistically estimate the directionality of the risk with a lot of confidence. And so I think the benefit is -- I'm certain -- not that it's clearly not there, but it's not clearly there.

Then in terms of the IPF-related mortality, I just think that although, on treatment, there was some suggestion of benefit, there were a lot of limitations to that analysis, as I've pointed out.

Also, I think from everything that we've heard today and the proposed mechanism of action of this drug as being an anti-fibrotic drug -- you want to get to the patients before they lose their lung function because it's not coming back -- if that indeed is the way that the drug is working, then the benefit really should persist after the drug is gone, because you've saved some lung, you hope.

So the fact that when you look at the mortality from on-treatment to the end of the study, when the patients may not necessarily be on the drug anymore, that benefit seems to lessen or go away. So I think that that argues against the robustness of the

data. That's a point I was trying to make, if that answers your question.

DR. CALHOUN: Dr. Krishnan?

DR. KRISHNAN: I have a question for the FDA, at least the statistical reviewer, if you could explain or comment on.

One of your slides seems to suggest that we should be wary of using the pooled results of the studies because of the lack of statistical significance in the primary endpoint in both studies. But as the committee is reviewing and trying to understand how to come to grips with what we've seen, we're being shown both the individual study results and the pooled results.

I wonder if you could clarify again what the agency's position is on the pooled results. Is it statistically not something we should be considering or is there some value in that, from your standpoint?

MR. ZHOU: What I am saying is the protocol is pre-specified. The applicant said if both studies showed significant at 0.498, then the pooled study is an analysis. But I'm saying only one study showed

efficacy. So pooled analysis results cannot be confirmatory. You can see it as an exploratory result, but not confirmatory.

MS. BUENCONSEJO: I want to add to that. And I think for mortality, it's a different story.

DR. CALHOUN: Could you introduce yourself, please?

MS. BUENCONSEJO: I'm sorry. I'm Joan Buenconsejo, acting team leader for statistics. For mortality, we would look at pooled data. And for the secondary endpoint that we said, the multiplicity adjustment, it's only for dose efficacy endpoints. For mortality, we would look at the pooled data and considered it important, confirmatory, if it's significant.

DR. KRISHNAN: If I could follow-up, I'm not sure I clearly understand the distinction here you're making between confirmatory and exploratory. I think I might understand, but help me understand, and perhaps others on the committee. Should we be not looking at it or if we should, what would you suggest, from the agency's standpoint, is the value that the

pooled analysis is providing?

MS. BUENCONSEJO: Tom? So for efficacy endpoint, because they did not win on the primary endpoint, for those secondary endpoints like 6-minute walk, not mortality endpoint, we will not consider statistically significant any pooled analysis. But for mortality, we would consider it if it meets the standard of statistical significance. I'm sorry if I'm not clear.

DR. CALHOUN: Okay. That'll be the last question for the morning session. We'll have ample time this afternoon to explore these matters.

At this point we will take a 50 -- that is five-0 -- minute lunch break, and we will reconvene again in the ballroom at 1:00 p.m. Panel members, please remember that there should be no discussion of the issue at hand during the lunch break, nor with any member of the audience. Thank you.

(Whereupon, at 12:11 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

DR. CALHOUN: Good afternoon, folks. We're going to reconvene.

At this point, we're going to proceed to the open public hearing. I will just say, as a point of order, at the outset, that we have a number of speakers, and we're going to ask that you stick by your time limitations assiduously, because we do have a number of folks who have been scheduled to speak.

Both the Food and Drug Administration and the public believe in transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, in the open public hearing portion, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you have with the sponsor, its product, and, if known, its direct competitors. For example, this financial information

may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting.

Likewise, the FDA encourages you, at the beginning of your statements, to advise the committee if you do not have such financial relationships. If you choose not to address this issue at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. And again, please respect your time limitations. Thank you for

your cooperation.

Our first speaker this afternoon is Joy McBride.

MS. McBRIDE: Hello. Thank you for the opportunity to speak today. I have no financial relationship with InterMune. Today, I speak for myself, my mother, my brother, my children, my future grandchildren, and my cousins.

It is appropriate that I speak to you in March, because March is a very important month to our family. My parents were married in March. I was born in March. My daughter was born in March. My dad was diagnosed in March. And he died in March 2008, almost three years to the day after he was diagnosed.

I asked my mother what she would like me to share with you all. This is what she said. Every time we went for a doctor's appointment, he always said the same thing. "You know, Mr. Woo, there is really nothing I can do for you." She said that was the hardest part, because it meant there was no hope, nothing that could possibly be done that would lengthen his life on earth.

You see, he was not just her husband. He was her eyes, because my mother lost her sight when she was about 50. My dad became her eyes, her transportation, her guide, her cook, her maid. He took over all the household responsibilities. They were inseparable, so losing him was quite difficult.

My dad's brother also died from IPF in 1992. I asked his daughter what she remembered. He died about a year after being diagnosed. She repeated almost the exact words that my mom and dad heard. "Mr. Woo, there's really nothing I can do for you." So from 1992 to 2005, nothing had changed for patients with IPF. Still no cause, no cure, no treatment, no hope.

I know medicine is a complicated field and advances are small and slow. I just ask today that you would give hope to IPF patients and their families. Thank you.

DR. CALHOUN: Thank you.

The next presenter is a joint presentation by Teresa Barnes and Lisa Richardson Waller.

MS. WALLER: Hi. I'm the first twin. My

name is Lisa Richardson Waller. And in the spirit of full disclosure, I just wanted to let you know that I graduated from the University of North Carolina at Chapel Hill, Dr. Koch. And while I was not compensated for my presence here today financially and I did not receive any basketball tickets, I am a huge North Carolina fan. I just wanted to make sure you guys were aware of that.

[Laughter.]

MS. BARNES: My name is Teresa Barnes. I'm her twin. And I am one of the founders of the Coalition for Pulmonary Fibrosis, a 501(c)(3). I also serve as the chairperson for the American Thoracic Society's Public Advisory Roundtable, which represents patient diseases and lung diseases of all kinds. I also serve on the American Thoracic Society board of directors and its board of trustees.

I do not have any financial obligations or commitments or any involvement with InterMune, although InterMune does do some work with the Coalition. I am not here, however, to represent the Coalition. I'm here to represent my family.

In the last 13 years, pulmonary fibrosis has reigned -- had a reign of horror over our family. Five members and an entire generation lost to pulmonary fibrosis, and every two and a half years since 1996.

MS. WALLER: Our father, his sister, and their three brothers lost their lives to pulmonary fibrosis, to this terminal and still untreatable disease. It threatens now our generation and that of our children.

MS. BARNES: Similar to serious diseases like breast cancer, pancreatic cancer, and leukemia, the incidence rate for pulmonary fibrosis is 40,000 deaths per year, 48,000 new cases per year.

MS. WALLER: One person dies of pulmonary fibrosis every 13 minutes. Right now, 128,000 people are dying in various stages of pulmonary fibrosis.

MS. BARNES: As mentioned, in 2010, Year of the Lung, designated worldwide, in the U.S. alone, 48,000 people will be diagnosed and another 40,000 will die.

MS. WALLER: In the mid-1990s, our father

went from doctor to doctor, but no one knew what was wrong with him. Finally, he landed at Duke University, and the kind doctors there were able to make the diagnosis.

MS. BARNES: Information and diagnosis has improved, but outcomes have not. More --

[Microphone timed out.]

DR. CALHOUN: Okay. Thank you very much.

Our next speaker is Sherry Miller.

MS. MILLER: Thank you for this opportunity to speak to you today. I have no financial relationship with InterMune, and I've not been compensated for my trip here. I just simply want to share with you how pulmonary fibrosis has affected my family.

In May of 2000, my husband's brother, Barry, was diagnosed with pulmonary fibrosis. He died six months later at the age of 47.

In 2005, my husband's brother, Ed, was diagnosed at age 54. He is no longer able to work, and he's on oxygen therapy.

My husband, Kim, was diagnosed in July of

2008. He began oxygen therapy last October. Over the last year and a half, I've watched my husband's health decline significantly, going from a man who loves to play softball, go hiking, to a man who has to stop after he climbs a flight of stairs. It takes him several minutes to recover after that. I see the look of frustration on his face. I see the anger sometimes, and I see the sometimes depression.

Our daughters, I see in their faces the fact that they know they're going to lose their dad far sooner than they should. And for us, since it's familial, we look at our children, who have to face the possibility of this disease. And we just simply ask that you consider that as you make your recommendations for approval for this drug. Thank you.

DR. CALHOUN: Thank you.

Our next speaker is Suzette Kern.

MS. KERN: Thank you for this opportunity to speak to you today. My name is Suzette Kern, and I'm here today advocating strongly for the approval of pirfenidone as a treatment for those with IPF. I have

no financial relationship with InterMune.

My family has the unfortunate distinction of being afflicted with the familial version of IPF. I've lost a brother, a father, a grandfather, and an aunt to IPF. Another brother, two years older than me, is currently living with IPF.

When a family member gets diagnosed with this disease, it is frightening, because there is no hope. The statistics for life expectancy after diagnosis are grim, with the end of life expected in two to four years. Right now, there are no real effective options, other than lung transplantation, and for those lucky enough to receive a transplant, life expectancy is again short -- another three years, with a whole host of different and difficult medical problems.

In June of 2003, two of my brothers were diagnosed with IPF. At the time, one was 53 years old and the other was 54. One brother, Larry, followed the expected course for IPF. His lung functions deteriorated rapidly, and within a year, he needed and was lucky enough to receive a lung transplant. The

transplant extended his life for four years and ten months. He passed away last month from complications.

The other brother, David, living today in Dallas, was fortunate enough in December of 2005 to get into the early access program, by lottery, for pirfenidone. Testing was already underway at Dallas and U.T. Southwestern for this drug, and he became part of that program.

It is not a cure, but after nearly seven years he is still alive. Though his lung functions continue to deteriorate, it was only last year that he began using oxygen on a regular basis.

Pirfenidone has worked for David. It has slowed the progress of this frightening disease. It offers hopes not only for David, but for the next generation in families like mine. I strongly urge that you approve --

[Microphone timed out.]

DR. CALHOUN: Thank you.

Our next speaker is Jim Puglise.

MR. PUGLISE: There was supposed to be a thing for the slides. Thank you.

First of all, in terms of disclosure, when I was diagnosed with IPF about four years ago, the first thing we did was buy about a thousand shares of InterMune stock. The assumption was if the medication worked, I'd make a lot of money. If it didn't work, I don't need the money. So that's kind of where I'm coming from.

[Laughter.]

MR. PUGLISE: You can't take yourself too seriously, I guess. My name is Jim Puglise, and I was diagnosed with IPF about four years ago. I participated in capacity 2, and upon completion of the study, was informed that I had been on pirfenidone 2403 for the entire study. So my total time on the drug is coming up on three years, and I continue to take it.

I also have a master's degree in health care administration, and have owned a company which analyzes health care data for approximately 20 years now. I'm not, however, a pulmonary expert.

First, in terms of lung function, lungs deteriorate normally at approximately 2 percent a

year. So this rate is actually a gold standard. The capacity studies used change in FVC as -- a percentage of predicted FVC as a preliminary endpoint.

There is another important lung measurement that was not in the primary endpoint in the study, and that's DLCO, which is diffusing lung capacity. I need to move along. So in terms of results, I wanted you to see what had happened.

FVC for me, on the drug, has decreased, and it's now decreasing at about 5.5 percent a year, which is about three times normal. DLCO is increasing [sic] dramatically. It's decreasing at about 8.3 percent a year.

That's unacceptable. I mean, it's different when you say 10 percent is a good target. But when you're a patient and your lungs are decreasing at 7, 8 percent a year, it's decidedly not good news. So DLCO was not included as a primary endpoint, and in my case, at least, has decreased rather rapidly.

[Microphone timed out.]

DR. CALHOUN: Thank you.

Our next speaker is Bernadette Sneed.

MS. SNEED: Hello. I am Bernadette Sneed, with the Better Breathers Club, and I came here to speak to you today on the struggle of not being able to fight pulmonary fibrosis.

We are all offered life, liberty, pursuit of happiness. I had my life as a respiratory therapist, and I worked at the Richmond VA Medical Center. I took care of people with lung disease since I came to Virginia in 1993.

I have two children that were in college. I had support from a wonderful disabled husband. I did everything I needed to do to support us all. I took care of my family, because we are team. I said I wasn't going to cry. They get their education, and I will take care of them.

But then I got sick. I am short of breath. I got to be on oxygen. Sad, defeated, stressed, anxious. My son had to quit his last year in college. My daughter graduated just prior to getting ill. She has not been able to get a job in Richmond; you know, all the people are losing their jobs. And they all have to take care of me and my husband.

We need help bathing, driving, grocery shopping, cleaning. Will I ever get to see them get married? Have children? Be a grandmother? No cure for what I have, not even something that will get me back to what I have. And my prognosis is poor.

We are in an age where life-threatening diseases such as AIDS or cancer may not have a cure, but they have hope because they have a way to help them fight their disease.

If this medication is safe, I'm asking you to please pass this medication to help me get my life back. Thank you.

DR. CALHOUN: Thank you.

Our next speaker is David Sanders.

MR. SANDERS: Thank you. My name is David Sanders. I'm from Richmond. And I suffer from pulmonary fibrosis. I may have to say I also -- I have a Ph.D. from Chapel Hill, so if that disqualifies me, I'm sorry.

I was diagnosed with the disease in 2003. Since most people with the disease die within three to five years, I'm one of the luckier ones, even though

my health is compromised and I'm on oxygen, in that I'm still alive, even though I've apparently had the disease since about 1996.

Since I've been too healthy and too old for a lung transplant, I've been awaiting a viable treatment for the disease. Consequently, I've followed with interest the history of pirfenidone, even before it was approved in 2008 in Japan.

I'm told it worsens in stages by acute exasperations [sic] -- that's not the right word -- whatever. One never knows when the next stage will come. I've experienced that reality already.

I spent my life as a college professor, and I'm on the board of Richmond Shakespeare Theatre. I would love to teach a course in Shakespeare at the local senior center on the plays being presented by the theater group, but I don't have the lung capacity or the stamina to do so.

I'm also a co-facilitator of a support group for people with lung diseases. I would love to have the ability to shoulder my half of the load for that group, but I don't.

It's difficult to see the walls closing in and not have any means of escape. Pirfenidone would seem to be relatively effective for some people caught in my situation. If it could indeed be useful without serious side effects, I hope you would see fit to give it your approval. Thank you.

DR. CALHOUN: Thank you.

Our next speaker is Thomas Spivey.

MR. SPIVEY: Hi. I'm Tommy Spivey from Wilmington, North Carolina. I'm 70 years old, a family man. I got one granddaughter, another one on the way. I would like to live long enough for them to remember me.

I was diagnosed five years ago at Mayo Clinic with IPF. I am a determined, self-made man. Owned seven businesses in seven cities in three states. I got an 8th grade education. Got over a hundred employees.

Because of my success, I was able to travel to Japan last year and got pirfenidone. Today my progress has stopped. Before taking the medicine, I was concerned with the side effects. My doctor told

me I'd have itch, rash, and lose weight, which Ray Charles could see that didn't work.

[Laughter.]

MR. SPIVEY: Or the itch or the -- I have no side effects. We live in this great country. Yet even with a known treatment, thousands of people die every year of IPF.

I'm not here to speak for myself, but for the people that's going to get it tomorrow and that's already got it today. We need something for them. I and thousands of others in this country would like to live.

While we will all die someday, it shouldn't be lack of a known treatment. I ask you to please take immediate steps for pirfenidone. Please give us hope. Thank you.

DR. CALHOUN: Thank you.

Our next speaker is Diane Dorman.

MS. DORMAN: Good afternoon. My name is Diane Edquist Dorman. I'm vice president for public policy for the National Organization for Rare Disorders. I have no personal financial relationship

with InterMune. From 2003 to 2005, however, NORD did administer an expanded access program on behalf of InterMune for pirfenidone.

I am here today not on behalf of InterMune or the therapy under consideration by this advisory committee. Rather, I am here on behalf of the millions of men, women, and children in the United States affected by one of the 7,000 known rare diseases that, in the aggregate, affect approximately 30 million people.

Rare disease research and the development of orphan therapies to treat them are unique in many respects. Patient populations are generally very small and geographically dispersed across the United States, Europe, and Asia, and few researchers and biopharmaceutical companies are willing to take on the financial risk associated with this vital work.

For those reasons and many more, NORD has been dedicated to helping people with rare or orphan diseases and assisting the organizations that serve them. Today, there are nearly 350 orphan drugs and biologics that treat only about 200 rare diseases.

Given that there are thousands more rare diseases without any specific treatment, it is easy to understand that there are millions of people who can only hope that, one day, someone will take on the significant financial risk to develop a therapy for their condition.

As you deliberate today, I ask only that you keep in mind that patients affected by rare diseases are willing to take on a far greater degree of risk than those affected by more readily understood diseases affecting larger populations. Thank you.

DR. CALHOUN: Thank you.

Our next speaker is Pamela Fetsch.

MS. FETSCH: Hello. My name is Pamela Fetsch, and I do not have any involvement whatsoever with InterMune.

I lost my best friend of 30 years, Dr. French Jackson, to this dreadful and always fatal disease, September 22nd, 2009. As you are aware, he and the victims of this killer die a terrible death. He was diagnosed in early July of 2009, and dead September 22nd, 2009.

The treatment of prednisone was useless. His primary doctor seemed to be unaware of this disease, and was looking to his heart as a possible source of his unusual lung sounds, crackling sounds. His heart was not the problem.

This disease kills 40,000 people every year, the same amount as breast cancer, however, with much fewer federal -- sorry about that; I'm short -- with much fewer federal and private research dollars allocated to its cause and its treatment.

The diagnosis of this terrible disease has risen 156 percent since 2001, with little recourse for treatment and victims dying within two to four years. My friend was three months.

Incidentally, it is expected to hit New York City residents heavily as a result of the destruction of the Twin Towers. Many first responders of 9/11 are now suffering and will die from pulmonary fibrosis. Some of the rescue dogs have already died or are suffering from lung cancer and unusual lung-related diseases. To date, the only possible life extender or cure is a lung transplant. However, it's not

available to everybody.

Many doctors are ignorant of this disease and prescribe useless steroids in the hope that it will reduce inflammation and stop the scarring. It is not COPD. All it seems to do is make the victims suffer more.

Some current research points away from autoimmune disease and inflammation of lung disease as the causative agent. Some doctors seem --

[Microphone timed out.]

DR. CALHOUN: Thank you.

Our next speaker is Jim Uhrig.

MR. UHRIG: My name is Jim Uhrig. I live in Pittsburgh, and I have no association with any of the sponsors of this product.

Two years ago, I was having difficulty breathing and felt like I had the flu for the best part of the previous two years. The good fortune of a bad cold forced me to my primary care doctor, who suspected more than just a cold. He sent me to a pulmonologist, who diagnosed me with pulmonary fibrosis.

I made two calls on the way home that day, the first to my wife, who searched the internet and printed off a couple hundred pages of information on the disease and treatment options. The second was to a friend who had a double lung transplant in '97.

My friend, Sully, connected me with the Simmons Center at the University of Pittsburgh Medical Center for my care, treatment, and introduction to the professionals dedicated to the research of this disease.

Since the beginning, my attitude has been the good fortune I had to know I was sick, why I was sick, understand the unknown clinical course of my IPF disease, and hope that none of my four sons and two grandsons from my blood line had my same fate.

I was blessed with getting to know the Simmons personnel and learning about many ideas and drugs used to treat my condition, until my double lung transplant last April.

I went from carrying an oxygen tank like this to coming home from the hospital two months later without the need for this tank, and back to work full-

time in my day job last fall and part-time in our family business.

The fate of a generous donor gave me new lungs, which came to me just in time. But my confidence in the medical staff, their competence, and my strong support of friends like Sully, my family, and other friends gave me the encouragement and the courage to win this battle for my return to a productive life, and possibly the opportunity to help others similarly afflicted.

Thank you.

[Microphone turned off.]

DR. CALHOUN: Thank you.

Our next speaker is Adam Schoeberlein.

MR. SCHOEBERLEIN: Good afternoon, and thanks for the opportunity to address the committee. My name is Adam Schoeberlein. I don't have any financial relationship with InterMune.

I'm not here to address quantitative data or medical efficacies or the scientific fitness of pirfenidone to receive any official stamp of approval. I really don't know anything about that stuff.

But here is what I do know. I know that in January 2004, I received a call at work from my wife in which, between sobs, she told me that her 74-year-old mother, Joan, had been diagnosed with IPF, an illness that the law of averages said should take her mom's life in about two to four years.

I know that we had just had our first and only child, a son, seven months before, and that while we tried to stay optimistic, we at times succumbed to morbid thoughts about what Joan might or might not live to see.

Would she live to see our son walk? Most likely. Would she live to see his second, third, fourth, perhaps even fifth birthdays? Would he remember her? We had researched IPF, and we knew what was and wasn't likely.

I know that about a year later, in May 2005, Joan entered the pirfenidone trial, and everyone breathed a sigh of relief, with the caveat in the backs of our minds that it was this or nothing. Pirfenidone and positive thinking was basically all there was, and that's been her cocktail ever since.

I know that as the years have passed -- six now -- Joan has become reliant on an oxygen machine, and that she avoids stairs as much as possible. She carries the mobile oxygen unit with her. She had it with her at brunch last month as the whole family, 20 strong, celebrated her 80th birthday together.

I also know that even now, in 2010, Joan drives to our house to visit with us, and to hear from our now almost 7-year-old son about his first grade adventures, to hear him play the piano, drums, and guitar for her, to sit politely as he demonstrates for her his video gaming prowess, and, most importantly, to dote on him and leave him with memories of a wonderful, loving grandmother.

I don't know if pirfenidone made that possible, but I know it didn't hurt. Thanks.

[Microphone timed out.]

DR. CALHOUN: Thank you.

Our next speaker is Kaitlyn Bergan.

MS. BERGAN: Good afternoon. I have no relationship, financial or otherwise, with InterMune.

My name is Kaitlyn Bergan. I'm 26 years old

and I grew up in Rochester, New York, being very close to my parents, Tom and Diane, and my younger brother, Danny. I don't need a photo of my father today to display, because I look just like him.

My dad became short of breath during normal daily activities. The specialist presumed his issue was cardiac in nature, but after a year or so of testing, no cardiac problem was detected. My mother, a med school professor and a very persistent woman, insisted on a pulmonary referral. It was only then that my father was diagnosed with pulmonary fibrosis.

I saw him, a proud, otherwise healthy and athletic man, with a long, successful career, be forced to retire, become dependent on oxygen, and ultimately not be able to hold a conversation or walk up the stairs. We had a hard time talking about it, as he had a hard time grasping the idea that he would miss out on the lives of his children that he gave everything for. And I had a hard time imagining a life without him.

It became sadly evident that our well-respected physicians knew very little about IPF, its

symptoms, prognosis, and care available. There were no support groups, and very little hope. We were out there on our own. He was admitted to Cleveland Clinic to receive a lung transplant that he desperately needed; however, he passed away on Valentine's Day of 2006 before it became a reality.

His death certificate read cardiopulmonary arrest, which we officially had switched to the real killer, pulmonary fibrosis. How many others are misdiagnosed, and how many death certificates hide the reality of how commonly devastating IPF has become?

I can't help but wonder, if he was correctly diagnosed to begin with, might I have had a few more years with him. Unless awareness is raised, not only in the medical community but in the public at large, and drugs like the one that we are here discussing today become available, this disease will continue stealing valuable years, valuable and meaningful years, from families.

Please give us some hope. Thank you.

DR. CALHOUN: Thank you.

Our next speaker is Mary Lou Rocha.

MS. ROCHA: First of all, I have no financial relationship with InterMune.

All of you have heard of death row. My name is Mary Lou Rocha, and I have idiopathic pulmonary fibrosis. I have been condemned to the same fate as those on death row, even though I am innocent of any crimes.

I'm a wife, mother, grandmother, and great-grandmother. One and a half years ago, my husband and I were bike riding, bowling, taking 4-mile walks, and now that is all out of the question, as I do not have the energy or breath to do so. I can no longer help my husband with his garden, which is something we both enjoyed.

I have the complete support of my husband and family. It has been hard on my husband, and he has been trying to help me. But there is no help out there for IPF patients other than a lung transplant. I have been told I'm not eligible for any clinical trials or a lung transplant due to my age.

At the time when I was diagnosed with this disease, the severity of it was not explained to me.

I am urgently pursuing the criteria for a lung transplant with the help of my support groups, the Inland Empire IPF support group and the One Breath Foundation.

It has been very hard on my children, as I cannot always do things with the family, and I won't be around to comfort them nor help them in their time of need. I am afraid I will not be around to see my grandchildren and great-grandchildren grow up.

Instead of making plans for family holidays and birthdays, I am now making my final funeral arrangements.

[Microphone timed out.]

DR. CALHOUN: Thank you.

Our final speaker for the open public hearing phase is Timothy Cooney.

MR. COONEY: Good afternoon. Thank you for your time. My name is Timothy Cooney. I am here on behalf of my family.

My grandmother died of IPF, and two and a half years ago, my father was diagnosed with IPF. My father is Donald Cooney. He was a neurosurgeon in the

area, fairly renowned. He was chairman of neurosurgery at the Washington Hospital Center, on the cover of the Washingtonian Best Doctors -- you get the picture. He was a pretty healthy person. But nothing could prevent him from inheriting the disease that his mother had.

My dad was lucky. He went on the ultimate campaign. He got a lung transplant. And as he used to joke, if I got to go around and pitch another, you know, 37-year-old guy who looks like you to get a transplant, I don't know what I'm going to do, joking because he'd been around the industry for such a long time in medicine. But it was still very tough for him to go through that.

Transplants are expensive. And I have children, my brother has children, and my sister has children. We're also just not confident that in 10, 15 years, even the transplant option might not be available.

I address the committee -- I know the issues that you're dealing with. I worked in the White House for three years over 10 years ago. You're dealing

with political risk. And I just have to say that I think for those families that are suffering from this, they'd rather just have that option.

I understand that, from your perspective, if a drug is approved and something doesn't work out, you may not want to have it happen on your watch. But to make an analogy, I think people who are leaving a drowning ship, if the life rafts have a couple of holes on it, they're willing to take that risk.

So I thank you for your time today, and please give your thoughts to the families and those that continue to suffer with the disease.

DR. CALHOUN: Thank you.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience.

The committee will now turn its attention to address the task at hand, careful consideration of the data before the committee, as well as the public comments. And again, we thank the speakers for their perspectives.

We'll now begin the panel discussion portion

of the meeting. This portion is open to public observers, but public attendees may not participate, except at the specific request of the panel.

So Dr. Karimi-Shah showed us the five questions earlier this morning, and we're going to take these questions in order. I would just remind the committee that there are several purposes for this discussion.

One purpose is for us, as a committee, to have questions and considerations addressed so that we have the fullest degree of information possible so we can make an informed decision. But a second and very important aspect of this is for the conversation to discuss the rationale behind our thinking, which will help the agency as they're pulling their thoughts together.

So with that, Dr. Chowdhury, would you like to charge the committee, or shall we just press on?

DR. CHOWDHURY: You can just press on. Thank you.

DR. CALHOUN: Okay. Dr. Knoell?

DR. KNOELL: So what I'd like to bring up is

it seems very clear, from hearing from both sides, that a few years ago, it was perhaps the wish of the FDA that if a trial was to be done, the primary outcome would be mortality. And the company, after deliberation, decided that that would not be the primary outcome, that it would be other outcomes which we've heard about today.

So as a panelist, I am really struggling with this dichotomy of what the two sides wanted initially and what they agreed upon. I'm also asking myself, if a mortality study was done as a primary endpoint study, what might that study look like in terms of numbers of patients, time, resources.

I think I probably need to hear from both sides on this issue, if I may.

DR. PORTER: Thank you. I think I'll comment first on that, and then defer to FDA and Dr. Chowdhury.

We certainly strongly considered a mortality study back in 2004 when we designed the clinical development program. I think, as we've heard today, it was our feeling and continues to be our feeling

that patients with mild to moderate disease, before they have irreversibly lost more lung function, are most likely to benefit from an intervention. And so we felt it was important to study patients with mild to moderate disease.

At that time, we were not sure we could do a mortality study. The only data that was available was from the SP2 study. There were a total of two deaths in that study. So we had no ability to power or design a study, and the natural history data, also, around the mortality rate was extremely limited.

What we did have was data on a very clinically meaningful endpoint of forced vital capacity from the SP2 study. And so we did have discussions with FDA, as have been characterized, and, at the end of the day, we decided, given that we weren't able to do a mortality study at that time, that FVC was the next most appropriate endpoint.

DR. CHOWDHURY: Maybe I can just comment to that, and after I'm done, I'll ask my colleagues if anybody wants to add anything here.

Dr. Karimi-Shah, in her presentation,

outlined some of her early discussion with the company on this product, and agreed with the company what they're saying here. And it really is a very, I think, challenging study to do with a mortality endpoint. But we had that on the table, and not really excluded that possibility, because from the presentations you have heard, it seems like the mortality is pretty high and the time to mortality is between two to five years.

If you look at most of the patients -- and during the study, they already had the disease going on for a year or more. And they're in the study for over one and a half years.

So ideally, what a mortality study would look like would probably enroll patients at some point. And given the drug's mechanism of action, which is still putative, you probably would not want to enroll patients pretty early on and then have long-term studies. Given the two- to five-year mortality, you probably would likely do a study equating for three years and longer and have a mortality endpoint.

The company chose not to do that, which is

reasonable and understood. So in that situation, we had to go with something which is clinically meaningful for the patient. And looking at FVC, it really is, in some way, a surrogate endpoint.

The question really becomes surrogate of what? And if it was a surrogate of mortality, are we really there to call FVC as a surrogate of mortality? And we are not sure if we can make the conclusion either this way or that, and we are taking it back to you to give us opinion.

Also, the point here is that we have seen a 10 percent cutoff being linked to clinically meaningful endpoints, such as mortality and 6-minute walk. Here, it's a smaller number. But again, it is a benefit.

Another issue that comes up is in a situation where you're looking at a measure such as FVC or some other measures, typically the agency has wanted replicate findings to ensure that we are not putting a drug in the market which may not really have the benefit that it is claimed to have.

We are here in a situation where one study

is showing benefit, and, as we have heard and discussed, mortality not going in the wrong direction. And still we're putting it back to you to give us advice.

So that is basically what my summary is of the discussions that we had on our thinking. And I'll invite anybody else from our side if they want to add anything. Banu and Dr. Seymour? Nothing to add. Thank you.

DR. CALHOUN: Let me take a stab a question No. 1, the efficacy. It looks to me as though the evidence in study 004 is strong, with improvements in vital capacity. And in my view -- and my view is as a doc who takes care of patients with IPF -- my view is that the shift in the distribution of FEV-1 responses in pirfenidone versus placebo in study 004 is both meaningful from a clinical perspective, and, obviously, it's statistically significant. And so that is a strong piece of information.

Now, looking at the FDA guidance on what represents substantial evidence is where we kind of bump into the problem in that study 006 didn't

replicate. I would kind of argue that the designation of one particular outcome as primary and others as secondary is somewhat semantic. And let me explain what I mean there.

This is unlike an outcome in which the primary outcome is necessary for any of the subsequent secondary outcomes to be meaningful. In this case, there are a number of outcomes, and there was some evidence that any of those -- like 6-minute walk, mortality, vital capacity, oximetry on exercise, just a number of potential outcomes that might have been relevant -- and the selection of one of those, the distribution of the forced vital capacity declines was selected.

But the fact that that one was selected, in my view, doesn't mean that the secondary outcomes would be invalid if the primary outcome weren't met. In my view, I think the agency's point of view on study 006 is probably too narrow, particularly given the fact that this is an uncommon disease, and there aren't that many patients that can be enrolled in trials. And so doing a trial of a magnitude in which

you could really have it powered up to do mortality would be extremely large.

So I'm saying I'm not sure that we should throw out the information in study 6. That's throwing the baby out with the bath water, in my view. I think there is some important clinical information in study 006, which, in many regards, is supportive of -- not duplicative of, not confirmatory in the technical and statistical sense -- but supportive of the benefit that was seen in study 004.

As I think Dr. Platts-Mills mentioned earlier, with respect to the mortality data, number one -- I think the sponsor mentioned this close to the outset -- the study was not and in fact could not be powered up on a mortality outcome. It wasn't big enough to do that. And so the fact that they missed a mortality outcome doesn't surprise me.

But I think it is intriguing that all of the mortality metrics were in the direction of favorability for pirfenidone. And moreover, the magnitude of the effect size was kind of similar, in the 40 or 50 percent range.

So I'm not sure that we know enough -- as was pointed out by Ms. Zhou, I'm not sure that we know enough to say that there really is a mortality benefit. There may be, if you look at that on-treatment IPF-related death. But maybe not. But certainly the weight of evidence suggests to me that there probably is benefit to pirfenidone treatment with respect to mortality.

Dr. Terry?

DR. TERRY: Yes. I've been looking at these curves of the FVCs, and the 006 and 004, the group that got pirfenidone, they're nearly superimposable on each other. And I think if the placebo group were the same for both of them, as it is in 004, this would be a much easier decision. There'd be a statistically significant difference.

But there's a marked difference in the two placebo groups. And the question is: Which one of those represents the truth, or do they both represent the truth? And I'd like to hear from both sides their explanations for the divergence in these two placebo groups.

DR. PORTER: I'll ask Dr. Bradford to address that issue.

DR. BRADFORD: They certainly are different, and I wish I could tell you which one reflects truth, and I wish I could tell you why they are different. We cannot.

I think that's one of the reasons that we have looked at pooled analyses, not for purposes of statistical inference, but for purposes of estimation, given the differing results, particularly at week 72 in their primary endpoint analyses, because they are helpful in that regard.

DR. CHOWDHURY: I think you posed the question for both sides to answer. So let me take it from the FDA side, which basically is we tried, and tried to look hard to see if we can find explanations, and we could not. If we did have an explanation, we certainly would have told you here.

We are very cognizant that the two placebo arms looks very different, and asking the same question also that you are posing, is: Which one is the truth? And we hope you can help us in that in

some way. Thank you.

DR. CALHOUN: Yeah. Pete?

DR. TERRY: The next question I wanted to ask relates to my observation that it appears that most of the benefit related to pirfenidone occurred between the initiation of the study and roughly between the 24th and 36th week. And then after that, the slope of the curve for the pirfenidone group appears to slope downward.

I was wondering, from a mechanistic point of view, what you all thought was an explanation for that, because the greatest divergence, as I see it, is early on in the study, and then it's parallel to the placebo group.

DR. PORTER: Certainly agree with that characterization of the graphs. I'm going to ask Dr. du Bois to comment on -- from what we know about the disease and mechanistic issues.

I'd just like to comment first to say that to us, the important observation is that the effect that is observed by week 24 or 36 or so persists throughout the end of the study while patients remain

on pirfenidone. So whatever the effect we're seeing early on, it's durable in the sense that it continues, as long as patients are on study and on drug, through week 72.

I would like to ask Dr. du Bois perhaps to comment on the mechanistic question you're asking relative to the pathogenesis of the disease.

DR. DU BOIS: Thank you. Can I, first of all, declare for the record that I have been a paid consultant for InterMune for the last 10 years, and have provided similar services for Actelion, Boehringer Ingleheim, Mondobiotech, and Centocor.

It's inevitably going to be speculative, but my concept of this is that, as I tried to show earlier today, there's a lot of disease that is fixed injured, fixed fibrosis, which experience with CT scan comparisons, for example, shows that that does not reverse.

So the concept, which I think is plausible, which needs to be tested is that pirfenidone is acting on this more nascent pathology before it becomes fixed and entrenched. And that potentially could explain

this divergence at that time period.

But the pirfenidone is not yet the complete answer for the treatment of this disease, so there are other processes that continue to progress -- the more aggressive fibrogenesis component, perhaps, from the entrenched fibrosis, which explains the continuing separation, because any new injury, potentially, is being abrogated by that continuing pirfenidone effect.

Now, as I say, this is speculative and will need to be put through the test. But it's a possible explanation. And one sees -- I'm not an expert, but one sees this sort of separation in studies of COPD, for example, where you get an effect which is then maintained.

Just one final point that I hope might support this argument is although it's a different index, we see exactly the same type of separation at exactly the same period of time on the 6-minute walk distance in the 006 study.

So to me, that's too coincidental not to be giving us a signal. And as I say, we're not smart enough to know the full answer to that yet, but I

think possibly this is a plausible explanation.

DR. CALHOUN: Dr. Platts-Mills?

DR. PLATTS-MILLS: Can I go back to my question that I half-asked this morning, which is about rebound? That is, is there any rebound after the end of treatment? Which is a little bit related to whether acute, accelerated decline occurs in this same form in patients who are on treatment.

We heard one speaker this afternoon say that he felt as though he had flu the whole time. Surely that could be worked out in terms of a cytokine. And really, in the same theme, you say that Imuran has been tried. But in the early work on Imuran, there were different attempts to use it in different ways. And we've ended up, unfortunately, with 100 milligrams a day, which is boring.

There are much more aggressive regimes where you can use 300 milligrams four days a week. Has anyone pushed to try and see whether, if this disease doesn't respond to steroids and doesn't respond to aggressive immunosuppression of other kinds, it leaves you very lost as to what you're trying to treat. And

that's an important question.

DR. PORTER: If I might, Dr. Platts-Mills, I'll respond to the first part of your question. And perhaps, if you'd like, Dr. du Bois can comment on what's been tried in terms of immunosuppression.

With respect to rebound effects, what I can say is that when patients come off pirfenidone in a relatively short period, there's no evidence whatsoever of a safety issue from a rebound standpoint. Unfortunately, there were two groups of patients that came off the study.

One group discontinued early, as we talked about, for adverse events or other reasons. That's obviously a biased group to interpret, but there were no safety signals in that group.

With respect to patients that came off study when we ended the study, we offered them the opportunity to enroll in the extension study, and over 90 percent of patients chose to do so. So they're on open label drug, and we can't use them to address the question you've asked.

I'd like Dr. du Bois perhaps to talk about

the immunosuppression, if he could.

DR. DU BOIS: That, again, is a really pivotal question. Thank you for asking.

The data are not great, because there have been no large studies of this. But working in London for many years with my mentor, where we did use quite aggressive -- my mentor, Margaret Turner-Warwick -- we did use quite aggressive immunosuppressive therapy for this disease -- and indeed, she published a paper on a smallish number of placebo-controlled patients -- with cyclophosphamide.

We do not see this effect. I, when I continued her work, also tried aggressive chemotherapy with intravenous cyclophosphamide for this disease. Again, no effect at all.

So I think what we're seeing is -- and I acknowledge there is more than a little bit of anecdotalism in what I'm saying -- but I've not been convinced that we've ever had a major impact with aggressive immunosuppression, which is what makes this drug so different. We've never seen this step apart at this 12- to 24-week period that we've been talking

about with any other therapy, including aggressive immunosuppression.

Just to complete the answer, we've also done it with aggressive corticosteroids. And of course, all that does is just gives aggressive side effects.

DR. CALHOUN: Dr. Karimi-Shah?

DR. KARIMI-SHAH: Dr. Platts-Mills, just to address one of your concerns regarding azathioprine, there is currently a clinical trial ongoing looking at the combination of inositol, cysteine, azathioprine, and prednisone together sponsored by the NIH. And details of that are available on ClinicalTrials.gov.

I'm sorry I don't have all of the details regarding that. But just because you did bring up the issue of azathioprine, this is being looked into and studied in a regressed fashion as we speak.

DR. CALHOUN: So one of the things that I think would be helpful to the agency is if the panelists would talk a little bit about the clinically meaningful effect size for change in vital capacity.

It does seem to me that what we've learned about changes in lung volumes, FEV01 and vital

capacity, in the obstructive lung diseases are probably completely uninformative to changes in the fibrotic lung diseases. I don't know that for sure, but I guess I wouldn't make the presumption that we can translate what we understand from obstructive diseases to the restrictive and fibrotic diseases.

So in that regard, I think Dr. Noble made an important point this morning, which is that there isn't a great deal of range. I think, Paul, you said it didn't run from zero to 100; it runs from 40 to 80. And so a loss of 10 percent in vital capacity makes a difference with respect to functioning, makes a difference with respect to the distance of the 6-minute walk, and, as was presented this morning, is a mortality predictor.

So I'm not certain that the change in the percent predicted vital capacity between groups is as helpful as the change in the distribution, the number of people who do and do not achieve a 10 percent decline in lung function. But perhaps we could talk about that point just a little bit, because I think that was one of the questions that the agency wanted

some guidance on.

Dr. Carvalho?

DR. CARVALHO: There's still one point here in the data that I'm still trying to figure out, whether the patient populations in 004 and 006 were indeed comparable.

We're looking at a lot of parameters. The agency has actually compiled a slide, on page 5, which looks at some of these parameters, which compares the two studies, and also has compiled the fact that there's a big difference in the number of patients that were on supplemental O_2. There were less patients in 004 than in 006. And this makes me wonder.

We can look at DLCO. We can look at function. We can look at it in many different ways. But when you look at actual gas exchange, were the patients in 006 perhaps a little bit more advanced, and is that why the results in 006 were different?

DR. BRADFORD: [Off microphone] the proportion of patients on supplemental oxygen used at baseline.

Slide up, please.

Here's a summary of the baseline covariates that had some degree of imbalance across the two studies. We've already talked about the first one there, diagnosis of IPF within one year of study entry, supplemental O_2 use, as you mention.

There was also an imbalance in the proportion of patients that needed oxygen to complete the 6-minute walk test. And this was under kind of a formal oxygen titration procedure, so it's a much more kind of precise estimate of oxygen need than whether or not a patient is on oxygen. Because this was a multinational trial, there are certainly regional differences in the proportion of patients using oxygen. And lastly, the geographic issue, which we've already touched on a little bit.

On the first, I can tell you, as we showed before, there's a statistical interaction that perhaps helps explain some of the 006 data. The supplemental O_2 use itself does not interact with treatment and does not appear to be a strong predictor of FVC change.

So we do not believe that the imbalances there, the 17 versus the 28, for example, are

relevant, nor are they an explanation for the differences in the outcomes at week 72 on the primary endpoint analysis.

The proportion of patients that needed O_2 during the 6-minute walk test, as you can see, is very small, and it's a relatively modest imbalance, at best. So we also don't believe that that is a strong reason for the week 72 differences.

DR. CALHOUN: Actually, Dr. Terry, I was going to call on you spontaneously, and Dr. Krishnan, as two clinicians who deal with IPF patients, to comment on this lung physiology issue.

DR. KRISHNAN: Thanks, Dr. Terry, for fingering me.

[Laughter.]

DR. KRISHNAN: So I think what you're trying to ask us to do is go back to the question, which is what change in FVC might matter. I think so far, the discussion has gone through that point to other points and come back around, I think.

I think the bottom line is it's not so clear, which is the reason why we're meeting as a

group, of course. I do agree with you that I'm not so sure that we can transpose the FVC or FEV-1 criteria from obstructive lung diseases such as asthma or COPD to this condition. I think there's lots of reasons why one should be careful in applying those metrics.

But with regards to the FVC, I guess I might think of it as what amount of change is something more than I would expect just by random error or measurement error that I might see. And for that, I might rely on some of our experience as we have run different pulmonary function test labs, and I've been involved in a variety of other clinical protocols.

There, when you have more than a 2, 3, 4 percentage change, that tends to occur just from measurement error alone. So I tend to not worry too much about a few percentage points, because it seems to be just an artifact of measurement.

I think when you start to get 10 percent more, that feels, to me, beyond what you would be able to have found just from measurement error alone. Now, I'm being very careful in how I'm saying this. I'm talking about that this is beyond sort of what I

expect just from repeated measurements.

I think what we really need to understand is whether that 10 percent change relates to some clinical parameter that patients actually would feel better with, whether there's a clinical meaningfulness, if you will. And on balance, I probably would err on the side of thinking that that's probably getting to the ballpark where I expect there could be other changes, from a patient-centered outcome standpoint, that patients would start to benefit.

But I think you're looking at one pulmonologist's view. I think there's not enough data to be very precise on this. And I'd be very interested in knowing what my former colleague, Dr. Terry, would say.

DR. TERRY: I think I agree with Dr. Krishnan that we'll, in our laboratories, accept a 5 percent variation as simply the variation of doing testing over and over again. And so this significant amount is something beyond that.

I think the answer is we don't know the

answer to what is a clinically meaningful effect size. One thing that has bothered me about this is, however, the fact that in the two experimental groups, if we look at common adverse events, dyspnea, which is the hallmark of IPF, as many of our speakers have so eloquently described it -- the two most common complaints that we see in our IPF patients are chronic cough and dyspnea, and dyspnea is usually the thing that limits everyone's mobility -- the dyspnea is twice as common, two to two and a half times as common in those who got pirfenidone as in the placebo group.

So I'm struggling with trying to decide how can the vital capacity be a meaningful effector or evidence of longevity when their primary complaint is twice as common in this group.

DR. KRISHNAN: If I could add to this discussion here on the FVC. So I guess what I've tried to lay out, and I think Peter agrees with me in large part here, that a 10 percent change probably seems to be something more than you'd expect by measurement error alone.

The thing that's troubling to me, though, is

that you have another identical study that didn't find an effect. And the lack of consistency bothers me, because if it's a real effect, it ought to happen again as you do the experiment again. The only way it wouldn't happen is that if the experiment somehow was bungled, didn't make the measurements right or something, which seems unlikely to me.

The other possibility is the patients were different, and we've seen a few slides where that it suggests there were some real differences between the patients that perhaps had crept in as you were enrolling study subjects.

But that brings me to the larger point that we're demonstrating in one efficacy study what I think is a real effect, another efficacy study no effect. And reconciling this makes me think that this drug probably works, but in some subset of people with this particular condition.

If we can't come to terms in understanding which subset benefitted, then I worry a little bit about potentially opening the possibility of widespread use of a drug in which the harm-benefit

ratio may be less clear, in fact, actually, there may be no benefit. But now you're exposing people to harm.

So I guess I would say that -- to answer your question more carefully, Dr. Calhoun, I would say that I think a 10 percent change, to me, I feel, is probably real and worthy of using as a mark, with some understanding that we're using the best available information at this point. But the fact that it wasn't confirmed worries me. There's heterogeneity of effects, and that we need to be careful that we're not exposing people to harm without benefit.

Now, one other point, if I could ask for clarification to the study sponsors, is that as part of efficacy studies, you very carefully select patient populations into your study. In fact, in most studies that I've seen conducted, it's a relatively narrow population you actually enroll for a variety of inclusion/exclusion reasons.

Could you comment on what proportion of people screened for IPF actually made it through and were enrolled? That might give me a handle on how

generalizable this information that we're being asked to consider actually is. So I guess what I'm asking is: Of people who meet inclusion criteria, what proportion were actually excluded because of various exclusion criteria? And how does that compare in 004 versus 006?

DR. PORTER: So I want to answer your question first, and then I need to make a clarification.

I don't have screening data to answer your question directly. What I can tell you is that we did have other exclusion criteria. They were primarily around patients with significant co-morbid conditions that were not stable, so cardiac lack of stability, et cetera.

In addition, patients with transaminase elevations greater than 2.5 times the upper limit of normal were all excluded. Otherwise, patients, in general, were allowed into this trial if they met the criteria. But I don't have the specific numbers that you're asking for.

DR. KRISHNAN: I'm sorry to just jump in,

but I just want to have a response to that. The reason, to me, that's important is because if we're trying to apply this information, trying to understand what the public good would be from this drug, I would need to understand a little bit how selected we ended up becoming as we studied this drug.

Most patients, or many patients with IPF, have more than one condition. It's very rare that that's all the problems that they have. So that might be something worthwhile pulling up, maybe, to help us understand this.

DR. PORTER: Okay. I'll ask my team to work on that.

While we're doing that, if I might just clarify, Dr. Terry. With respect to the dyspnea issue, dyspnea was reported as an adverse event in 19 percent of patients that received pirfenidone and in 22 percent of patients that received placebo. I believe Dr. Karimi-Shah commented on that when she presented this morning, that there was an error on the slide.

DR. KARIMI-SHAH: Yes. I apologize for

that, Dr. Terry. On that slide -- I believe you're referring to my slide 32 -- in the placebo column, that figure should read 20 or 22 rather than 10. I apologize for that error.

DR. PORTER: If I could make a further comment, Mr. Chairman? With respect to some of the points that have been raised, we certainly appreciate the challenges of interpreting FVC and understanding it, largely because it's been difficult to do trials in IPF.

One of the advantages of having been doing these trials for 10 years is that we have a substantial database that doesn't exist elsewhere. And probably many of the committee members are familiar with the previous development problem, which was discontinued due to lack of efficacy with Interferon gamma, in which we enrolled over 1,000 patients in clinical trials.

We've been able to use that database to address the very question that's being discussed. And if you would allow us just a couple of minutes, I'd like to ask Dr. Weycker to summarize fairly briefly

what we've learned.

DR. CALHOUN: I think that's probably responsive to this question.

DR. WEYCKER: Derek Weycker. I'm a health economist at PAI. We've been involved in a number of studies on behalf of InterMune over the past six to eight years.

To better understand this issue of clinical significance or clinical meaningfulness, we undertook analyses to ascertain the measurement properties of FVC and to estimate the minimal clinically important difference for this measure.

As was just noted, we used the clinical trial data of interferon-gamma, and this particular population included a total of 1,156 study subjects.

The results of our analyses suggest that FVC is a reliable measure -- slide up -- as indicated by the correlation coefficient of .93 between proximally temporal measurements of FVC. And we see the mean interval between measurements was 18 days.

The results of our analyses also suggest that FVC is a valid and responsive measure in patients

with IPF. This conclusion is based on the reliability coefficients that you see in the upper left-hand corner of each panel, as well as the way in which change in FVC tracks with changes in the other measures that were considered: 6-minute walk distance, the SOBQ, DLCO, and SGRQ.

In addition, the results of our analyses suggest that FVC is important in its association with mortality. Slide up. In these analyses, we found that patients with changes as small as 5 units, declines in FVC as small as 5 units, had a more than twofold increase in the risk of death; and that patients who had declines of 10 or more had a nearly fivefold increase in the risk of death. I'm sorry? This is absolute units. That's correct, in percent predicted FVC.

In addition, we estimated the MCID, which is the minimal clinically important difference, for FVC using a number of different published methods, including distribution-based and anchor-based. Distribution-based include the standard error of measurement in the effect size, and the anchor-based

include the patient-referencing and criterion-referencing approaches.

As you can see, there's robust consistency across the various approaches utilized to estimate the minimal clinically important difference in FVC, ranging from 2.1 to 5.8. Thank you.

DR. CALHOUN: Okay. Thank you.

Dr. Shah, I guess, is the next on the list. No? Okay. Dr. Knoell?

DR. KNOELL: I want to come back to this. It's especially timely after seeing these slides. So several panelists over the course of the day have brought back the notion of quality of life measures, and I still remain confused on this. Maybe I missed some of the information, but my understanding is that you used potentially three different quality of life measurement tools in this study. And you just showed us data from another drug, a different trial, that those type of metrics correlated really well with FVC.

So far, if I'm not mistaken, what we've been told is there are not really good measurement tools for quality of life specific to pulmonary fibrosis,

which I agree with, but yet some were used.

Is the message that I get correct that there were no statistically meaningful differences in quality of life measures across these two studies comparing the active treatment and placebo?

DR. PORTER: That's correct with respect to the pre-specified analyses. And we did look at three instruments. And I think it's an important point, and I'll ask Dr. Bradford to review that with you.

DR. BRADFORD: Could I have the slides up, please?

Here's a complete summary of all the secondary and exploratory endpoints that were looked at in the 004 study. As far as the PROs go, dyspnea -- you can see it with the 6.1 down or so, measured by the UCSD SOBQ. These are standardized treatment effects.

No statistical significance. I presented some data earlier about a post hoc analysis at the tails of the distribution, suggesting maybe there's some effect.

We also looked, towards the bottom there,

two of the last three on the table under exploratory endpoints, we looked at the St. George respiratory questionnaire, and we also looked at the HRQOL, and neither of those provided evidence of a benefit.

Another way of looking at this data -- could I have slide SS-91?

So as efficacy outcome measures, there was no evidence of benefit, although the point estimates tended to go in favor, particularly of dyspnea.

Here's an analysis analogous to what Dr. Weycker just presented based on the pooled data from the 004 and the 006 studies, namely, if we look at placebo patients -- so independent of treatment effect here -- is there a relationship between FVC decline and dyspnea, as measured in this study with the UCSD SOBQ and decreased exercise tolerance, as measures with the 6-minute walk test.

As you can see there, there's a fairly strong signal telling us that, in fact, when patients drop their FVC by 10 percent, they do experience more dyspnea and have decreased exercise tolerance.

DR. CALHOUN: Thank you.

Dr. Foggs?

DR. FOGGS: I'm not sure what actually constitutes clinically effective change in delta FVC, as we've heard multiple discussions about the parameters that would affect the impact of lung function on these patients with IPF.

But notwithstanding that particular effect, we've also heard about the importance of quality of life. We have no specific parameters to delineate what constitutes improvement in quality of life, because the questionnaires that have been mentioned in passing were not specifically designed to look at this particular disease.

Having said that, I'd like to get back to what was said earlier by Jerry with regards to the heterogeneity of the disease requiring us to look at specific subsets and specific, perhaps, genotypes. We know that in the 004/006 studies, that there was a discrepancy, with one study showing an positive outcome as it relates to use of the drug, and another study, 004, showing a positive outcome [sic].

To that extent, it would be interesting to

me to determine whether or not the genotypes of those individuals that constitute the subjects in each respective study has been thoroughly analyzed.

In our audience, we had multiple participants who spoke, pointed out the fact that they have experienced, in their families, IPF on the basis of familial predisposition. And that predisposition undoubtedly is associated with some genetic discrepancies.

Could there be polymorphisms for the drug in question that have not been ascertained, and are any studies designed in the making, especially with any additional longitudinal studies, to address this issue?

DR. PORTER: Thank you. That's an important question. We did collect DNA samples from the Phase 3 trials. That's a future analysis that we plan to do. There are complexities, of course, with what's understood around the genotypes.

But it's a very interesting and important question. And again, I'd like to ask Dr. du Bois to comment on this issue of genotypes and familial

disease.

DR. DU BOIS: Yes. Thank you. Indeed, I think this is a tremendously important question.

As you know, there are a number of genes that have been associated with familial disease, and these appear to be rather private mutations. So there are a series of mutations in the surfactant protein C gene, for example, one of which may run through one family, another of which will run through another family. But the outcome issue is the same. And there are also studies of telomerase.

I think, more importantly, trying to get more precisely at your question, we will be, at National Jewish under David Schwartz's leadership, be doing a GWA study of all of the capacity and the interferon-gamma patient studies to try to get to your question of, is there genotypic heterogeneities. So I think that's a crucial issue that is in the future plans.

If I could just make one other comment that speaks to heterogeneity. I think that I'm getting a sense we're presuming that this, in some way, is a

phenotypic heterogeneity. But it is possible that it is a longitudinal behavior heterogeneity that we're seeing between the studies, and that, for whatever reason, as Dr. Bradford has said, we just can't explain.

But perhaps, for some unknown reason, we had a group of individuals who were behaving longitudinally phenotypically differently rather than necessarily this being a subset of IPF at the genetic or histopathologic level.

DR. CALHOUN: Dr. Terry, you're next on the list. Okay. Dr. Hendeles?

DR. HENDELES: So I have a question and a comment. The question is: Did the sponsors check the packaging to see if there was an error in the blinding of 006? I've had that happen, where a pharmacy technician has mixed up labeling. I'll let you answer that first, and then I'll have my comments.

DR. PORTER: I, too, have had that unfortunate experience in a previous study. So we did check very carefully, and there's no issue there. I would also point out that the results were very

consistent between the two studies up to 48 weeks.

DR. CALHOUN: Dr. Krishnan?

DR. KRISHNAN: Sure. I wanted to, Dr. Calhoun, perhaps go back to the question you'd asked, because I think the slide SS-20 that has just been put up by the sponsors might help illuminate what's a clinically significant change in FVC.

So there are many ways to identify a clinically significant change. But one way to think about it, perhaps, is that was the change in FVC that we saw in study subjects -- does it hang with other patient-reported outcomes? And did those PROs also move in the direction that would suggest to us we've found something that helps people?

The reason I think that's an important slide -- and in fact, I'd suggest putting it back up, if it's possible -- is that I was struck with the public comment with patients and family members and others individuals, the burden that this disease imposes on patients.

To me, it seems to me I've never really heard of a patient come to me that says, "My FVC has

dropped." They usually tell me, "I can't breathe, or I can't walk up the stairs, or I can't do what I need to do."

So I was struck with this particular slide that suggests that if we leave aside the FVC change for a moment, there is a significant, statistically significant, difference there. If we go to the PROs, they're in the same direction, but they seem not to exclude -- no difference, meaning that at least from a patient burden standpoint, we don't see it hanging together with the FVC change.

I wanted to know if the sponsors could comment on why they're seeing this. Is it because we have the wrong instruments, or is it that the FVC change was not commensurate with other health burden parameters that we might have?

DR. BRADFORD: I can't give you a specific answer to your question other than to, I think, state what's already been discussed several times today, which is all three of these instruments are ones which have not been really validated in the context of IPF. And actually, to go a step further than that, most of

them have never been used and really analyzed in a way that would shed a lot of light on the validity.

I'll also make a point that's been made earlier in that change in this disease is unidirectional. And a lot of these instruments are used in diseases where patients both improve and get worse. And perhaps one of the challenges here is that, one, nobody gets better; they're only getting worse.

As we've seen from the FVC data, particularly the categorical analyses broken out at 10 percent, a significant proportion, roughly two-thirds of patients, do not drop their FVC 10 percent at 72 weeks.

So as you're looking at the distribution over time and who can drive these instruments, who can drive the signals, really what we're seeing here is a third of the patients, and certainly the ones with the most pronounced drops, but those at the greatest risk for the bad outcomes, as well, are the ones that are driving these signals.

So it becomes a relatively small number of

patients with respect to looking at these unvalidated instruments and gaining insight into how they're performing here.

So I think it is important to recognize that none of these estimates go in favor of placebo over pirfenidone. And while they certainly don't -- the PROs don't hit nominal p values, they are leaning in favor of the drug over placebo. So there's no evidence of harm with respect to quality of life or health status measured by the St. George.

DR. CALHOUN: Dr. Honsinger?

DR. HONSINGER: That slide answered part of my question, and that is that we're focusing on the forced vital capacity. And yet you had data on the total lung capacity and the diffusion capacity.

In the 004, that correlated very well. Does that correlate well in the 006 study, as well, or do you have enough patients that had those studies?

DR. BRADFORD: You are correct that the FVC changes in the 004 study are -- we see similar changes on TLC measured with plethysmography as an exploratory endpoint.

Incidentally, we did not present that because it is an exploratory endpoint. But the AA gradient, which is obviously a very objective endpoint, as well, shows a similar magnitude of effect in the 004 study directionally.

In 006, at week 72, there was not a treatment group difference. And we see a relatively similar finding on both the TLC and the AA gradient endpoints there. Earlier in the study, where we do see activity on FVC out through week 48, for example, in the 006 study, we also see changes in treatment group differences and TLC.

DR. CALHOUN: Dr. Mauger?

DR. MAUGER: I'd like to make two points. One is that in terms of what we've been focusing on, we've talked several times about inconsistency between the two trials with respect to FVC. I'm not sure they're really all that inconsistent.

Dr. Porter was just saying a minute ago that, actually, in more than half of the outcomes, it was a statistically significant favor for pirfenidone over placebo. It happened to be not significant at

the end. In addition to that, when you average over the entire trial and the repeated measures, the results were very similar between the two trials and highly significant in both.

We've also asked what's going on with that placebo group in the 006 trial. One thing I think we ought to be careful of is why should we assume that they would not diverge again? They diverged early on in the trial, and then they converged again. But I'm not sure why we should assume that they would not diverge again, and that 006 wouldn't show an effect had we followed it farther out.

That might fit along with this idea that the placebo group in the 006 study is sort of behind the 004 group in the progression of their disease. We saw that there's a significantly higher fraction of patients with a more recent diagnosis, and I would take that to mean that those patients have had less time for their FVC to deteriorate.

So I would think we would expect to see that placebo in the 006 go down in a way that would match sort of the 004 at an earlier time.

DR. PORTER: You raised several incredibly important points. I'd like to just take a second on one of them, if I could.

At the risk of showing you a complicated figure, which is in your briefing document, but I think it makes one of the points that you just did -- slide up, please.

It is certainly true that in the primary outcome at week 72, 006 failed to replicate 004. But in many ways, these studies are much more consistent than they are different. And in many ways, they replicate each other over different time points and across different endpoints.

What this graph is showing is the numerical directionality, if you will, that's going to show -- and I show you the data -- the numerical directionality of each outcome over each assessment period for both studies for both the primary endpoint, the secondary endpoints, and survival.

If you could build, please? The open circles here show the instances where the outcome numerically favored placebo, which is, as you can see,

only four out of at the 78 outcomes.

Could you build again, please? The solid circles show where the outcomes across all these endpoints and at each time point favor pirfenidone. And the two circles show where they favor pirfenidone with a normal p-value of less than .05.

So I would agree with your comment that, overall, these studies are much more consistent than they are different, although I acknowledge that, at week 72, we have a different outcome.

DR. CALHOUN: Dr. Hendeles?

DR. HENDELES: So my assessment is that the effect, if it's real, is very modest. And in looking at the post hoc analysis of the IPF-related deaths, the confidence interval for each of them include an upper limit of 1.31, which means there's a potential 30 percent chance that the drug could increase mortality.

On the other hand, if you look at slide 22, where they pool the same data, it very clearly has a low hazard ratio with a confidence interval that's less than 1. So I think in terms of that particular

endpoint, which is clinically extremely relevant, there seems to be support for efficacy.

DR. CALHOUN: Well, thank you.

I would like now to turn the focus of our discussion to question 2. And this is the discussion of the safety data. If important issues come up with respect to efficacy in that context, we can certainly deal with that as well.

Dr. Hendeles?

DR. HENDELES: So I have some real concerns. This is a theophylline-like product, in my mind. It reminds me of it in terms of its pharmacokinetics and bioavailability and its metabolism. And I think no one would argue that the adverse effects in the pivotal studies were probably underestimated.

In fact, they didn't use a valid method of measuring adherence, so you don't know if there were patients who were poorly adherent, and that underestimates adverse effects.

For one thing, the metabolism by cytochrome P4501A2 is subject -- the gene that expresses that enzyme is subject to polymorphism. And there can be

patients with very long half-lives, with caffeine and theophylline using that same enzyme pathway. The fact that there are drug interactions -- there are over-the-counter products like cimetidine, Tagamet, that inhibits that enzyme pathway. And that could be a hazard.

The other thing is while we know that all the studies were conducted with food, we don't know what happens when a patient doesn't take it with food, whether that increases adverse effects or whether there's any higher blood levels.

There is a higher peak level, which would suggest that there's more rapid absorption when it's taken fasting. But I don't know what the implications are, and I think there's some concerns about the potential safety.

As far as the dangers with hepatic dysfunction or renal dysfunction, those probably -- since this is going to be handled by a specialty pharmacy and presumably only specialists in this disease are going to be prescribing the drug, I don't think that that's probably as big a problem.

But the overall biopharmaceutic profile, I think, places this drug at a potentially higher risk.

DR. CALHOUN: Point of order, then, from Dr. Chowdhury?

DR. CHOWDHURY: I just wanted to draw your attention that for question 1, we actually had two elements. One was FVC for discussion, and the second one was the mortality.

We actually had a very healthy discussion on FVC, and thank you for that. And I was wondering if you were satisfied with the mortality discussion or do you want to go back to that at some point or, as we had the discussion already, if not, then you can consider that.

DR. CALHOUN: We had had some discussion on mortality. Dr. Hendeles summarized his view on mortality. We can talk about it again.

DR. CHOWDHURY: I just wanted to make sure that that's all you would like to discuss. Then that is fine. If not, I didn't want to break the chain of thought, which we're discussing the safety right now. Perhaps after that, we can see if there's anymore

discussion on mortality or not. Thank you.

DR. CALHOUN: Very good.

Dr. Knoell?

DR. KNOELL: A couple of questions, probably more directed at the sponsor. So I might have missed this earlier. But with respect to adverse profiling, GI intolerance, it's my understanding -- and tell me if this is correct -- that a lot of these patients with the dose escalation experience some irritability over the first few weeks, but that the majority of the patients ultimately prevail and tolerate the medication just fine. Is that correct?

DR. PORTER: It's certainly true that, in general, the tolerability issues, particularly with respect to GI, tend to decrease over time. So that is a correct statement, yes.

DR. KNOELL: Then related to photosensitivity -- and then I have one more thing after this -- with photosensitivity, my understanding is that it does have an increased risk. Therefore, every patient should be advised about the risk of photosensitivity.

My understanding is, from a colleague, that these patients are extremely sensitive; like, if they have a sunroof in their car, they have to be careful about exposure.

But it would be, I think, plausible that these can largely be avoidable if patients are educated appropriately. Is that your opinion?

DR. PORTER: It is our opinion. And in part, the data from the trial would suggest that that's the case, and to the point that the vast majority of cases of photosensitivity were single episodes that resembled a sunburn.

I think despite the fact that the protocol contained recommendations for sun protection measures, not everyone necessarily took those. But my suspicion is that they did after the first episode, because we did not see, by and large, recurrence of photosensitivity in patients.

If I might just address very quickly Dr. Terry's concerns, because I think they're significant concerns that I should speak to.

I think, with respect to pirfenidone, the

first important point to make is that, in general, the adverse events are tolerability issues and they're not serious safety concerns -- excuse me, I think it was Dr. Hendeles that made this comment -- and they're not significant safety concerns. They are primarily tolerability issues.

In addition, the profile with respect to those adverse events has been extremely consistent across all clinical studies that have been done. So while there may be some underreporting, it certainly has been consistent, and that's been true in the post-marketing experience as well.

I think the issue with respect to drug interactions is an important one. We looked at it in the study, and I'd like to share some data very quickly, or have Dr. Rubino share some data, that answers your question, or at least gives you what data we have on that.

DR. RUBINO: Thank you. I should probably clarify. It was mentioned to me at the break that it might not be clear. Our group has done contract research work for InterMune for the last six years.

So we do not have any equity interest, but have done contract work.

Can I have the slide up, please?

You mentioned theophylline and caffeine. And I can't really comment to all of the CYP enzymes that are involved in the metabolism of those drugs. But for pirfenidone, multiple CYPs do catalyze the metabolism of the parent compound, pirfenidone. CYP1A2 is the primary one, but others make up to 13 percent of the in vitro data.

What you're looking at here is information from a population PK screen we did in those 88 patients from PIPF004 that contributed PK sampling. On the Y axis, you have dose-normalized AUC, because there were patients from both dose groups; and on the X axis is weight in kilograms. And that's simply to spread the data out so you can actually see where the individual points are.

On the left panel, these are any patients -- essentially, the dots are colored based on whether or not the patients had concomitant administration of CYP1A2 inhibitors. The blue circles are weak to

moderate inhibitors, and there were several patients in there that got cimetidine, which you had mentioned. And the pink are strong inhibitors. In this case, it was primarily ciprofloxacin.

You can see that, in general, all that data is spread out very consistently across. And this isn't just early exposure to the drug. This is average over the entire study period. We had sampling throughout the study.

So based on this data -- and granted, it's just a screen; it's an exploratory analysis -- but we did not think there were any signals for major drug interactions from drugs that only inhibit CYP1A2. Remember, fluvoxamine inhibits multiple CYPs. So any of those enzymes that maybe can account for the metabolism of pirfenidone might be inhibited by fluvoxamine.

DR. PORTER: Perhaps you can also comment on the other concern that was raised if the drug is taken without food.

DR. RUBINO: Yeah. In the original food effect study, there was a significant effect of food

on the Cmax of pirfenidone. If we could have that slide up just so I can see the numbers, because I don't want to get that wrong. I believe it's 005, the two profiles. Go to the next one, please. Yes, that one. If you can just show it.

This is the mean profiles. It was a crossover study, so every patient got food or not. And you can see the Cmax is almost 16 when they didn't get food. Those are the two higher profiles. And when those same patients got food, the Cmax was only in the 6.5 range.

This was under very controlled conditions with a high-fat meal. When we looked at this in the multiple-dose study, where patients were just given a regular meal, the Cmaxs were lower, but it was somewhere in the middle there.

We don't expect that this huge Cmax difference would be observed with chronic administration if they missed, say, a day of taking it with food, or even if they were doing it over a fairly long period of time.

DR. CALHOUN: Dr. Knoell has one last

question.

DR. KNOELL: One last question, unrelated to the previous ones.

So you had mentioned to us earlier in the day that if this medication were approved, that you would close the channels, restrict those who can provide it to patients, and I think that's very plausible, given the circumstances.

With respect to that, I'd like to hear more from the sponsor how they intend to utilize that opportunity for continued studies, many in line with the kind of things we're talking about now -- post-marketing issue, drug/drug interactions, genetic variability that can influence response or toxicity.

DR. PORTER: As I mentioned earlier today, we do have two ongoing safety studies that we are continuing. And those studies collectively enrolled over 700 patients, and we continue to follow for safety.

With respect to the distribution chain, we currently have not designed any studies for that, and certainly open to considering that. Dr. du Bois

mentioned that we do have follow-up work with National Jewish Health on genotypes from this study to try to address that question.

But you are correct that having that type of distribution network gives us the opportunity to design follow-up studies, and we certainly would be interested in doing so.

DR. CALHOUN: Dr. Platts-Mills?

DR. PLATTS-MILLS: On the safety issue, I think it's very important to understand the difference between drugs that are being used in benign disease and drugs that are being used in a disease like this, which is clearly not benign at all.

I would remind people that there are -- the difference, say, between cetuximab and omalizumab. Omalizumab has an anaphylaxis rate of .1 percent, which is a major concern to us. And I'm on an academy committee where we're worrying about a .1 percent reaction rate.

Cetuximab is a cancer drug, which, in the South, has a reaction rate of 20 percent, which does not appear to be a concern to anybody, because it's

being used in an extremely dangerous disease. So it really matters what you're dealing with.

These side effects, and the description of the side effects and the definition of them that's been given to us today, talking as a physician, do not disturb me in the least. These are side effects that we are quite used to dealing with and perfectly happy to deal with it.

Liver enzyme 1, we're perfectly -- normal with a lot of antifungal agents that we use regularly. Monitoring patients like this is perfectly acceptable. The sunburn effect appears to be quite mild and not comparable in any way to what happens in Auckland, New Zealand when the ozone layer hole is over Auckland, when they have second-degree burns, so that I see nothing in these side effects.

Absolutely central to this, in many previous trials, people have shown a drug decreases the mortality from that disease. And everyone's very excited until they look at overall mortality and find that overall mortality has increased with the drug.

That is not the situation here. The

situation here is quite clear that in all the situations we've seen, the overall mortality has decreased with this drug.

So that I would say that the safety evidence that were offered here is very reassuring that this is -- on what has been done, obviously limited numbers; this is not a drug where you're going to get vast trials with large numbers. I think the safety issue is very clear.

DR. CALHOUN: Dr. Honsinger?

DR. HONSINGER: I agree with you, Dr. Platts-Mills, that a drug that had -- a third of the people got a skin rash, a tenth had some type of cardiac event, maybe just as simple as tachycardia, and a half had some type of GI or liver side effects, and yet had a very low dropout rate, I think people were able to tolerate these side effects.

The question I have for the sponsor is you did mention in your presentation, without exact data, of patients who had to reduce the dose of the drug for tolerability. How much did they have to reduce the drug? Was this a temporary thing? Were they able to

increase the drug back to full dose later on? What was the reduction in dose to accept tolerability of the drug?

DR. PORTER: Thank you. Could I have slide up, please?

So two slides just to help answer that question, Dr. Honsinger.

This shows the adverse events leading to dose modification by system organ class. And again, I would point out that any dose modification, including one-day interruption or one-day reduced dose, gets you counted on this slide.

As can be seen, the most common causes were, not surprisingly, gastrointestinal disorders and skin disorders, again, tolerability issues primarily. Just to clarify what the other SOCs on here represent, investigations is primarily a liver function test, so transaminases. General disorders is primarily fatigue, and nervous system disorders is primarily dizziness.

Could I have the next slide, please?

Again, to give you some idea of what the

significance of this was, as I pointed out in the presentation this morning, certainly, dose modifications were more common in patients treated with pirfenidone. This slide breaks it down by dose reduction, which is exactly what it sounds like, any reduced dose for at least one day, and dose interruption, which is a interruption for at least one day. And again, we see higher rates for both of these with respect to pirfenidone. Can you build, please?

If one looks at the median cumulative duration of that dose change, which is now shown here, you can see that the median cumulative duration on the bottom for dose interruption is comparable between the two. It's significantly greater in patients treated with pirfenidone at 70 days versus five days. But that 70 days is based on a median treatment duration of over 500 days, so it represents less than 15 percent of the average treatment duration.

So in general, while the dose modifications were common, they were typically temporary and short-lived.

DR. CALHOUN: Mr. Mullins?

MR. MULLINS: Back to the issue of the subjects with liver abnormalities. What was the outcome of the patients that did suffer from liver abnormalities or enlargement of the liver? Were they able to continue with the trials? The first question.

The second question: What adverse effects led to a discontinuation of participation in the clinical trial? Thank you.

DR. PORTER: So to answer your first question first, while we're pulling up a slide.

I tried to show some of the individual liver profiles from this morning to summarize that information with respect to what happened to those patients. First of all, all the liver enzyme abnormalities were reversible. Two patients were able to continue on full dose.

The remaining patients, one discontinued permanently, and all the remainder were able to continue on a reduced dose without subsequent abnormalities. And so those patients clearly were able to tolerate a reduced dose without a recurrence of their transaminase elevations.

Could I have slide up, please?

With respect to the adverse events that led to treatment discontinuation, and I think this came up earlier in the conversation, the fact that idiopathic pulmonary fibrosis was the most common cause. Again, that was investigator's coding of the adverse event that he or she attributed to treatment discontinuation. And again, next most common were, not surprisingly, GI and skin-type events. Again, relatively low rates of adverse events leading to discontinuation.

DR. CALHOUN: Ms. Gottesman?

MS. GOTTESMAN: While I agree with a lot of the concerns that are being raised, I completely concur with Dr. Platts-Mills. As someone who's taken Cytoxan and taken the Immurans, I look at this safety profile and I go, "Eh, not so bad."

I would like to see long-term safety data. That's one of my big concerns. I'd love to hear, again, what's happening with the open label studies. So that's my concern. But I look at this as a patient and say, "That's doable to compare to what's out

there."

DR. CALHOUN: Dr. Hubbard?

DR. HUBBARD: Yes. I have a question with regards to the mortality data. The FDA did a post hoc analysis and said some of the mortality data perhaps raised questions, because it perhaps wasn't consistent.

But my experience is that there's usually a very thorough analysis of every mortality within a clinical trial, including oftentimes getting the clinical chart from the investigator to review the mortality data, and conducting safety analyses by the safety physicians within the sponsor, and perhaps even having a blinded review of mortality data by outside people.

I wonder if any of that was done in this case with regard to the mortality data, and if there was any suggestion that perhaps the investigators were inconsistent with regard to their interpretation of causes of mortality.

DR. PORTER: There certainly was a thorough review of all deaths from a safety standpoint to be

comfortable that there was no safety concern.

In terms of actually looking at inconsistency or possible inconsistency of investigators, no. We did not do that, per se. We decided at the design stage of the trial that, given the complexity of these cases, that the investigator was in the best position to assess whether a death was IPF-related or not, which we defined as IPF made a clinically meaningful contribution to the death of the patient, and it was recorded on the case report form based on the investigator's judgment.

So that was the prospective way we collected. It's ostensibly the leased biased estimate. But we did not assess that issue with respect to the investigator.

DR. CALHOUN: Okay. So moving back to Dr. Carvalho. Sorry.

DR. CARVALHO: A couple of quick questions. First of all, could the sponsor describe the dose reduction protocol that you use in the studies?

The second question is: Regarding all the follow-up information that we're needing and wanting,

open label and information that's out there in patients on pirfenidone, the Japanese are ahead of us by about a year and a half. And there must be some information there that we could possibly apply to our purposes.

DR. PORTER: Let me answer your second question first, if I might.

There's lots of information there, which we continue to receive from that study on a real-time basis. Just to remind you of my earlier comments, over 1,400 patients enrolled in that study. And it's a post-marketing study; it's not a pharmacovigilance type situation. These patients are seen at 12-week intervals, and we get regular reports on the adverse events.

I'm happy to share data with you. I can tell you that the profile is absolutely what we've seen here. And we specifically look for adverse events of interest. You recall that list of 10 categories that I've shown.

We track those very carefully, and there is no sign of any concern whatsoever. And again, I'll

let you follow up; if you want to see that data, I'll be happy to share it with you.

Could you repeat the other part of your question? I apologize. Oh, dose reduction. Thank you. Dose modification guidelines.

DR. CARVALHO: Yes. Dose reduction protocol.

DR. PORTER: Thank you.

Could I have slide up, please?

So the dose modification instructions that were given to investigators were as shown here. In general, the dose modification was at the investigator's judgment for the more tolerability issues. One of the advantages of having three capsules three times a day is that one can titrate up and down, and that was partly by design.

So each time a dose modification was undertaken, the patient was reminded to take the dose with food, and also reminded of other precautions such as sun avoidance precautions, et cetera.

With respect to liver function tests, we did follow this closely. With respect to grade 1 or 2, it

really was at the clinical judgment of the investigator, and they could titrate by one cap t.i.d. all the down to a dose interruption. And as I mentioned when I went through those profiles, some of those patients did have dose interruptions, and then once the LFTs resolved, they were titrated back up.

If it was grade 3 or higher, we did ask that they discontinue study drug.

DR. CALHOUN: We're going to take one more comment from Dr. Honsinger regarding safety, and then we're going to move to Dr. Chowdhury's point of order.

DR. HONSINGER: Much the same question. You have the data on those people on long-term study. We should also have data from Japan, where they've launching patients on open purchase of the drug.

DR. PORTER: We do. Again, over 1,400 patients enrolled in that study in Japan. We get real-time safety data. We get SAEs in real-time. We get all adverse events monthly.

Could I have slide up, please? Since there's an interest in that data, I'll be happy to share it with you.

This is an overview of the adverse events that have been seen to date in the Shionogi post-marketing study. In general, you can scan this list and see that, again, this is an open label study. Obviously, there no comparator. You can scan this list and see that, in general, it's the adverse events that were reported in the SP3 study as well as in our study.

As I mentioned a moment ago, we do monitor the adverse events very carefully for the 10 categories of adverse events of interest and, again, there's no evidence of any abnormal signal in those 10 categories.

DR. CALHOUN: Okay. So Dr. Chowdhury asked us maybe to restate our views on the mortality efficacy data. Let me try to summarize what I've heard around the table, and then if I've gotten that wrong, please chime in.

So the mortality estimates, while, in general, not reaching statistical significance, all show point estimates that are in favor of pirfenidone. There's one mortality estimate, the on-treatment IPF-

related mortality estimate, that does reach statistical significance. And we recognize that the study was unpowered, underpowered, actually, to achieve a mortality estimate.

DR. CALHOUN: Dr. Knoell?

DR. KNOELL: Just a minor point of clarification, but from an earlier discussion with the agency, and that it is plausible in the scope of the mortality data to use pooled data from 004 and 006.

DR. CALHOUN: Mr. Mullins?

MR. MULLINS: Thank you. I just wanted to be clear with Dr. Shah that there was no clear morbidity benefit, correct, from pirfenidone. Mortality benefit.

DR. KARIMI-SHAH: Correct. What Dr. Calhoun says is true, although all the point estimates were less than 1, meaning that, numerically, they were favoring pirfenidone over placebo.

The confidence intervals were wide. And so as Dr. Zhou stated in her presentation, because of that wideness, the risk could easily also be in the other direction. And so we can't really know that

that point estimate is the true estimate with much confidence.

MR. MULLINS: You're making that statement based on the structure of the trial or the substance of the data?

DR. KARIMI-SHAH: I'm not sure what you're asking me. If you could clarify.

MR. MULLINS: Are you saying we have insufficient information, or just the structure, the nature of the trial, the number of participants?

DR. KARIMI-SHAH: I'm not sure what you're asking. The analysis shows that the point estimate is not -- that the point estimate is not statistically significant.

DR. CALHOUN: If I can just clarify what you're saying, or to try to get you two on the same page, it appears that there's at least an N issue, that is, a larger trial with that given point estimate. With a larger trial, the confidence intervals may have shrunk to the point that they did not include 1.

DR. ROSEBRAUGH: I think what she's trying

to say is just, to your point, there weren't enough events that we could comfortably say whether it would have shown an advantage or not. If it was a bigger study, to get to your thing, and had the same event rate, we probably would have been able to draw stronger statistical conclusions.

DR. CALHOUN: Okay. We're going to move on, then, to the voting questions. And we will be using the electronic voting system for this meeting.

Each of you have three voting buttons on your microphone, "yes," "no," and "abstain." Once we begin the vote, please press the button that corresponds to your vote. After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen, and I will read the vote from the screen into the record.

Next, we'll go around the room, and each individual who voted will state their name and vote into the record, as well as the reason why they voted as they did. And it's my understanding that the formal vote is actually what you say, not what you click in, although if you say something different than

what you click in, you probably need to explain that, too.

[Laughter.]

DR. CALHOUN: Okay. So Question No. 3 is a voting question, which is: Do the data provide substantial evidence that pirfenidone provides a clinically meaningful, beneficial effect in the treatment of patients with IPF to reduce the decline in lung function? And we'll deal with 3(a) in just a minute. So vote your vote.

[Voting.]

DR. CALHOUN: Do we have all the votes? Okay. So the results are yes-7, no-5, and abstain-0. So we'll run around the room, and we'll begin with Dr. Foggs.

DR. FOGGS: As I said earlier, I don't think that the data actually constitute what we can define as a clinically meaningful delta FVC. However, if we look at the pooled analysis of progression-free survival as a surrogate for the lack of specificity with regards to the absolute meaning clinically of the change in FVC, I think I'm willing to extrapolate to

the extent that, to me on a personal level, is clinically meaningful, notwithstanding the fact that the other question, which is extremely critical and essential to the interpretation of that concept as discussed, cannot be addressed in the form of health-related quality of life.

DR. CALHOUN: Thank you. Dr. Platts-Mills?

DR. PLATTS-MILLS: I voted yes, because I think that the changes in FVC which we saw are significant, and that they showed an important level of consistency between the two trials; and, that in the context of this disease, this is clearly a -- this is a clinically significant effect without a serious side effect that would discourage me.

DR. CALHOUN: Dr. Krishnan?

DR. KRISHNAN: I voted no, because I felt that the FVC data, which were the basis of the primary outcome, to me, demonstrated substantial heterogeneity, with one study demonstrating effect and the other one not so clear.

I was also struck by the absence of patient-centered outcome data that would help me feel better

that the measured differences in FVC were actually clinically meaningful.

DR. CALHOUN: Dr. Knoell?

DR. KNOELL: I voted yes. At face value, I was thinking no. I changed to yes, because over the course of the day, I think I've unequivocally seen that, overall, the metrics, it shows benefit even though not always statistically significant. And trying to keep in view of the larger perspective and what, basically, no options these patients have, I feel it's beneficial.

DR. CALHOUN: Ms. Gottesman?

MS. GOTTESMAN: I voted no. I feel that the unpredictable progression of IPF makes it difficult to measure whether patients are getting worse because of the treatment or due to chance. And I also question why it wasn't duplicated in 006.

DR. CALHOUN: Dr. Carvalho?

DR. CARVALHO: I voted yes, because I'm still not quite convinced that two populations in 006 and 004 are the same. And also, we're after a clinical effect over here, and I think I've seen

enough data presented today to convince me.

DR. CALHOUN: Dr. Mauger?

DR. MAUGER: I voted yes. I was convinced by my colleagues here that at an individual level, a 10 percent decrease in FVC was significant. And I think if you were to ask a patient, to tell them, "Over the next 16 months, you've got a 30 percent chance of a significant decrease in FVC, and with this drug, it's only 20 percent," I think that's substantial evidence.

DR. CALHOUN: Calhoun. I voted yes, and I did so because study 006 is convincing to me that there's a significant change in vital capacity, number one.

Number two, the data that were provided show that the change is more than can be attributed to chance alone, number one. Number two, the data we saw this afternoon suggests that the change in vital capacity is probably about twice of what it takes to be clinically -- a minimal clinically important difference.

Then with respect to the issue of

substantial evidence, and that's actually where I was wrestling earlier in the day, I was relieved by the fact that study 006 actually did replicate study 004 out through week 48. And as Dr. Mauger articulated earlier this afternoon, the repeated measures data also showed replication.

So I'm really less concerned about the formal lack of replication in study 006 than some others. And so I thought there is substantial evidence, and that it's clinically important, and that it's statistically significant.

Dr. Honsinger?

DR. HONSINGER: Honsinger. I voted yes. I had a difficult time, because of several reasons. The first, from the testimony we heard and from the -- we got a large volume of written testimony, as well, some people were expecting a cure. This is not a cure. I do not want to sell a false hope. This is something that cures a misconception of this drug; it just slows the decline of the disease. So that needs to be emphasized.

I think, second of all, that this is going

to have to take a closed distribution network. In my experience with my patients that are already on drugs on closed distribution networks, especially pharmacies that provide and promote the drug, it's very expensive. These patients end up paying 20 to $50,000 a year for pills. And so that's another reason to have some qualifications about voting for it.

The third reason is I think that we need more data. I think we need to find out the subset of data that the data helps.

We need to do that by analyzing the data. We need to do that by analyzing the serum, looking for genetic abnormalities, looking for inflammatory factors that might tell us the patient would get benefit, so we don't give it to patients that don't need it and won't get help from it.

DR. CALHOUN: Mr. Mullins?

MR. MULLINS: Thank you. I'm very concerned about what we do not know about pirfenidone. The largest body of information that we have was never submitted to the committee from Shionogi. We have not

seen any raw data, only qualitative data, no utilization data, which I think would be very pertinent to the committee. And I think it would be important to us to make a comprehensive, balanced decision.

Secondly, I think we never analyzed, or I was never given a sufficient response, as to why we never reached the desired endpoint in 006, the clinical trial. We did not win that endpoint. We did not reach that endpoint.

The other issue that concerned me as to why I made a no vote is that we had no clear mortality benefit. The last question I had to Dr. Shah, there's no clear mortality benefit. So thank you.

DR. CALHOUN: Dr. Terry?

DR. TERRY: I voted no. The question we were asked was: Does the data provide substantial evidence of a reduction in the decline in lung function? A reduction implies compared to something, and the comparison was the placebo group. And we have two conflicting pieces of placebo data.

I don't know which to accept as the truth

and, therefore, they're in conflict. And based on the agency's criteria for substantial evidence, I don't think that this then meets the criteria.

DR. CALHOUN: Dr. Hendeles?

DR. HENDELES: I voted no, because I don't think it meets the criteria of substantial evidence.

DR. CALHOUN: Okay. Thank you very much. Are there comments on Question 3(a)? Dr. Honsinger mentioned a couple of things, and I think Kristine had captured those. Are there other pieces of efficacy data that should be obtained, and in what context? Dr. Knoell?

DR. KNOELL: Well, I actually didn't like the way the question was worded because, as you know, I voted yes, but that doesn't mean that I don't want to see more data.

I think, from the patient perspective, we talked today about hope and -- real hope and false hope. And right now, I don't think it's very clear at all for a practitioner now being able to prescribe this medication, theoretically, that they would be able to tell that patient specifically the amount of

hope that they should have in terms of improving their pulmonary function or not, as well as any influence it may have on mortality.

So those two primary determinants, and some of these other metrics we talked about, I would like to see more information come through more studies for the sake of the patient.

DR. CALHOUN: Dr. Hendeles?

DR. HENDELES: I, too, would like to see data expanded, both on the safety and efficacy and, in terms of efficacy, in patients with an FEV-1 less than 50 percent predicted, because those are the ones I understand are at highest risk of dying. And so it would be important to see, in those patients, whether it has any benefit.

DR. CALHOUN: Dr. Terry?

DR. TERRY: I would like to see more rigorously collected mortality data.

DR. CALHOUN: Dr. Krishnan?

DR. KRISHNAN: I would like to recommend that -- the drug distribution system that has been described by the sponsor suggests to me there's an

opportunity to build a registry and to track patients over time. I think there is much to be gained by better understanding which patients are actually benefitting versus which don't. And obviously, you can't do an endless number of clinical trials to answer all those questions.

This is an opportunity to actually help us understand this. So my recommendation is that, if the FDA does approve this, that it would be worthwhile having a registry built in to understand what's happening in the real world.

DR. CALHOUN: Dr. Platts-Mills?

DR. PLATTS-MILLS: I was surprised that Dr. Terry and Dr. Hendeles both said that this doesn't reach the agency's criteria for substantial benefit. I don't know what the agency's criteria for substantial benefit are in this disease.

Also, I think that -- I'm not clear that we were told what those criteria were to be in this disease, so that I don't know why [off microphone.]

DR. CHOWDHURY: Well, I'm not going to answer for Dr. Hendeles.

DR. PLATTS-MILLS: No. The question was not for the FDA. The question was to those two members of the panel.

DR. CHOWDHURY: Thank you.

DR. HENDELES: I don't know what their specific meaning is. But it doesn't seem substantial to me. I think that a 4 percentage point difference and a lack of -- if you looked at that slide -- I think it was SS-20 -- with the exception of FVC, all of the other endpoints either overlapped 1 or touched 1. And so those were not -- none of those were significant.

DR. TERRY: If I recall correctly, there was somewhere in the introduction of the packet that I got that convincing evidence to the agency was suggested by two well-designed, placebo-controlled trials that found the same endpoint; or one trial in which the comparison between the placebo and the experimental group was so dramatically different that it was highly persuasive.

DR. CALHOUN: For the record, that was Dr. Terry.

Okay. Let's move on, then, to Question 4. This again is a voting question, which is: Has the safety of pirfenidone been adequately assessed for the treatment of patients? And -- to Dr. Knoell's point -- if or if not, what further safety data should be obtained?

So we'll vote.

[Voting.]

DR. CALHOUN: We need one more vote. Re-press your buttons.

[Voting.]

DR. CALHOUN: Okay. The results are yes-9, no-3, abstain-0.

So we'll begin this time with Dr. Hendeles.

DR. HENDELES: I already stated what my concerns were about the potential safety. And I agree that Dr. Platts-Mills brought up a very valid point, that this is a disease that is fatal, and so that those adverse effects that we've seen so far don't seem to be relevant. But does the word Vioxx mean anything to you, Dr. Platts-Mills? So I think the --

DR. PLATTS-MILLS: Yes, indeed. And exactly

that's my point. Vioxx was being given for very mild disease.

DR. HENDELES: Well, I think the solution is to have some program like they did for Xolair in terms of collecting safety data for a time period after its approval.

DR. CALHOUN: Dr. Terry?

DR. TERRY: I voted no, because I'm concerned about what Dr. Krishnan -- the question that he raised. And that was: From what large group were this selective group screened?

I'm concerned that in IPF patients, who usually are in their fifth, sixth, or seventh decade, who have so many co-morbidities, that the possibility exists that we will find, over time, some side effects that relate to those co-morbidities. And I'm concerned that some of those may have been screened out in these initial studies.

DR. CALHOUN: Thank you. Mr. Mullins?

MR. MULLINS: Thank you. I'm concerned about the insufficient data, and I believe that there is a need for more of a longitudinal study to look

more closely at safety. Thank you.

DR. CALHOUN: Dr. Honsinger?

DR. HONSINGER: I think the safety data that we have is adequate for this population. I think there's a larger population of idiopathic pulmonary fibrosis out there that this is not identifying.

We certainly see patients in our practices who we think may have pulmonary fibrosis that we don't try to diagnose it, because it's been a disease that we could not treat. So when it's mild, we wait until it gets more severe, until they get ready to -- or to the disease where they need an open lung biopsy to determine that disease.

I suspect that we're going to find a lot of patients who have mild idiopathic pulmonary fibrosis that may fall in this category. And those are the ones that may live longer, and we're going to have to watch more carefully for side effects of the drug.

DR. CALHOUN: Calhoun, and I voted yes, because I think, as Dr. Honsinger just articulated, for this population the safety concerns have been addressed adequately for me. That is certainly not to

diminish the legitimate and important concerns that Drs. Hendeles and Terry and Mr. Mullins have articulated.

I don't think the data set is complete for the real world population that may see this drug, and that appropriate post-marketing follow-up certainly needs to be done.

But for the population that was studied, I think the data, the safety data, are compelling to me, particularly with regard to the severity and outcome of this disorder.

Dr. Mauger?

DR. MAUGER: Mauger. I voted yes, for the same reasons that have just been articulated. We don't know how leaky the lifeboat is, but it's a lifeboat.

DR. CALHOUN: Dr. Carvalho?

DR. CARVALHO: Carvalho. I also voted yes. I think that we do have the luxury of additional data from the Japanese populations. And also, as raised by Dr. Krishnan, this gives us a very good opportunity to start a registry and get further information as time

goes on.

DR. CALHOUN: Ms. Gottesman?

MS. GOTTESMAN: I voted yes for all the reasons I stated earlier, although I do want to see the long-term safety data from the open label studies.

DR. CALHOUN: Dr. Knoell?

DR. KNOELL: I voted yes. And I'd like to expand upon Dr. Terry's comments. We talked about the uncertainty of how this drug behaves in patients. And by virtue of the study design, we probably selected out your average IPF patient, understandably so.

But an argument was made earlier, I believe, that by virtue of its redundant metabolism with multiple CYP enzymes, that it shouldn't be that big of a concern with drug/drug interactions, or maybe less of a concern.

My point I want to make is that by virtue of that, the drug itself, and in terms of, in the future, identifying responders from nonresponders, probably opens up much more variability because of the fact that this particular drug is metabolized by multiple CYP enzymes.

So I would encourage the company to do much more surveillance post-marketing, if it comes to that.

DR. CALHOUN: Dr. Krishnan?

DR. KRISHNAN: I voted yes. I think that the sponsors have done a good job of telling us and tracking what AEs occurred. But I think it's hard to know when you have enough safety data. You never have enough safety data. And so I would strongly urge the use of a registry to help us better understand this in the post-marketing side.

DR. CALHOUN: Dr. Platts-Mills?

DR. PLATTS-MILLS: I voted yes. I think I've made it clear what I think about it. I think the safety has been addressed adequately. I think, in the long run, post-marketing data will tell us whether this drug genuinely changes the mortality of the disease. I hope that we're able to show that.

DR. CALHOUN: Dr. Foggs?

DR. FOGGS: I voted yes. I think that the progressive debilitating nature of this disease eclipses the magnitude of the side effects that we've seen. And I think that the longevity of the patients

who suffer from this disease makes the potential side effects seen within the three- to five-year period we're talking about for typical longevity after diagnosis a secondary issue.

I also think this is a strong argument for doing additional genetic studies, as mentioned before, to try to delineate some of the polymorphisms and genetic discrepancies that exist in sub-populations.

DR. CALHOUN: Very good.

Let's move to Question 5, the last voting question. Does the committee recommend approval of pirfenidone for the treatment of patients with IPF to reduce the decline in lung function? If or if not, what further data should be obtained?

And then with regard to Question 5(a), I think it's fair to say if you've already articulated what further data need to be developed for efficacy and what further data need to be developed for safety, that's fine. These would be new things that are beyond what we've already talked about.

So we can vote.

[Voting.]

DR. CALHOUN: Okay. So the results are yes9, no-3, and abstain-0. Let me editorially comment, I'm proud of the committee that no one abstained. Not the vote -- I'm proud of the committee that no one abstained. We stood up and made the direction.

So we will begin our discussion with Dr. Foggs.

DR. ROSEBRAUGH: I would also like to thank everyone that no one abstained, either, because I have to sign this eventually and I can't abstain.

[Laughter.]

DR. ROSEBRAUGH: I do have a question, though, which would help me in my deliberations with this. So technically, for those folks -- and I didn't write down everyone's name; I just noticed that five voted that there was not substantial evidence that this provided a meaningful benefit, and yet only three voted to not approve it.

So for the two that voted no for question 3, but voted to approve it, I would like them to elaborate on their thinking behind that. Thanks.

DR. CALHOUN: Okay. We will do that as we come around.

Dr. Foggs?

DR. FOGGS: I think it's been well articulated that there's no effective treatment for this almost always fatal disease in the absence of an apparent atypical course that we usually see with IPF. And I think that this medication serves an unmet need. And it's not a perfect therapeutic intervention, but it helps fill the void and stem the tide.

As has been demonstrated by the pooled analysis of 004/006 studies, it actually is beneficial in inhibiting the progression of a decrease in lung function in terms of progression-free survival.

DR. CALHOUN: Before you speak, Tom, just as I'm counting the votes, the two, I think, that will need explanation are Ms. Gottesman and Dr. Hendeles.

Dr. Platts-Mills?

DR. PLATTS-MILLS: Yes. I voted yes, because I am convinced by the changes in lung function. And I believe that there's enough evidence to think that the changes in lung function are

specifically related in many ways to the disease and its harmful effects; and that I think if you do the calculations on decreasing lung function over a period of two or three years, a 4 percent difference is highly significant in the outcome at three years.

DR. CALHOUN: Dr. Krishnan?

DR. KRISHNAN: So I was just trying to be internally consistent. I was less convinced about the efficacy data. I was not so worried about the safety as much as some of my colleagues. And so I felt it difficult to balance the safety versus efficacy issue. And I've already stated my recommendations if the agency actually approves the drug.

DR. CALHOUN: Dr. Knoell?

DR. KNOELL: I voted yes. I have nothing further to add.

DR. CALHOUN: Ms. Gottesman?

MS. GOTTESMAN: I voted yes. And the reason I did is I've been straight the middle the entire time. And I think while I didn't see substantial efficacy based on the FDA regulations, there was clinical significance based upon the discussion we had

today.

I don't think approving a drug is based on one particular entity. IPF is a futile disease. I think you need to offer your patients hope. And if this can offer your patients a smidgen of hope, it's worth approving.

DR. CALHOUN: Dr. Carvalho?

DR. CARVALHO: I also voted yes, for several of the reasons that the panelists have already mentioned.

In addition, I would like to see some information, because I suspect that there might be the magic time at which we should start to administer this medication where it's most effective by virtue of its action.

So additional information other than FVC, looking at function, looking at gas exchange, looking at AA gradients, so that we can get everybody matched across the board, would be good information to have from now on.

DR. CALHOUN: Dr. Mauger?

DR. MAUGER: I voted yes, for the reasons I

voted yes for 3 and 4.

DR. CALHOUN: Calhoun. I voted yes, for the reasons that I voted for 3 and 4.

Dr. Honsinger?

DR. HONSINGER: I voted yes. Even though this drug will help a minority of the patients that will take it, I think we need information on when to start the drug. I also think we need information on when to stop the drug.

DR. CALHOUN: Mr. Mullins?

MR. MULLINS: Thank you. I voted no, because I feel that there was not compelling information that the therapy would benefit a large portion of the patient population. Yes, it did benefit a portion of the population, but I'm not convinced that the data was compelling enough for me to feel like it was an effective treatment for the entire patient population. Thank you.

DR. CALHOUN: Dr. Terry?

DR. TERRY: I voted no, for the reasons that I stated for questions 3 and 4.

DR. CALHOUN: Dr. Hendeles?

DR. HENDELES: I voted yes, which was opposite of my vote about substantial efficacy, because I don't believe it has substantial efficacy. But Dr. Shah's slide 22, which is the time to on-treatment IPF-related death, when they pool the data, it shows that it decreases the risk by 50 percent. And I thought to myself, if I got this disease, I would be on the next Delta flight to Japan.

DR. CALHOUN: Well said. Thank you.

So at this point we have completed our voting. And I want to ask the FDA if there are any other issues from the agency that bear further discussion or amplification.

DR. CHOWDHURY: No. We don't have any issues that need to be discussed here. I just wanted to make sure asking Dr. Rosebraugh. We don't have anything.

Since I have the mic, I just wanted to thank you, Dr. Calhoun, and other members of the committee for spending the time in reviewing the data with us and sharing your views and thoughts. This really is very helpful to us. Thank you very much.

DR. CALHOUN: So thank you very much to the sponsor for staying on time. Thank you very much to the FDA for their insightful analysis and presentations. And thanks very much to the committee. We're adjourned.

[Whereupon, at 3:27 p.m., the meeting was adjourned.]